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Potential Benefit with Complementary and Alternative Medicine in Irritable Bowel Syndrome: A Systematic Review and Meta-analysis

Wade Billings[1], Karan Mathur[2], Hannah J. Craven[3], Huiping Xu[4], Andrea Shin[5]

[1]Department of Medicine, Indiana University School of Medicine; [2,5]Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana, USA; [3]Ruth Lilly Medical Library, Indiana University School of Medicine; [4]Department of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana, USA

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Corresponding author: Dr. Andrea Shin, Indiana University School of Medicine, 702 Rotary Circle, Ste 225, Indianapolis, IN 46202, USA; email: ashin@iu.edu

Author Emails: [1]wabillin@iu.edu; [2]kdmathur@iu.edu; [3]hancrave@iu.edu; [4]huipxu@iu.edu

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ABSTRACT

Background and Aims: Patients with irritable bowel syndrome (IBS) may pursue complementary and alternative medicine (CAM). We conducted a comprehensive systematic review and meta-analysis examining efficacy of CAM vs. placebo or sham in adults with IBS.

Methods: Publication databases were searched for randomized controlled trials of CAM therapies (herbal therapy, dietary supplements, mind-body based, body-based, and energy-healing) in adults with IBS. Data were extracted to obtain pooled estimates of mean improvement in abdominal pain (standardized mean difference [SMD]) and relative risk (RR) of overall response using random effects models. Sensitivity and subgroup analyses along with quality assessments were completed.

Results: Among 2825 articles identified, 66 were included. Herbal therapy (SMD=0.47, 95% CI: 0.20 to 0.75, I^2=82%) demonstrated significant benefit over placebo for abdominal pain (low confidence in estimates). Benefit with mind-body based therapy for abdominal pain was of borderline significance (SMD=0.29, 95% CI: -0.01 to 0.59, I^2=78%). Herbal therapy (RR=1.57, 95% CI: 1.31 to 1.88, I^2=77%), dietary supplements (RR=1.95, 95% CI: 1.02 to 3.73, I^2=75%), and mind-body based therapy (RR=1.67, 95% CI: 1.13 to 2.49, I^2=63%) showed benefit for overall response compared to placebo (low confidence in estimates). Body-based and energy healing therapies demonstrated no significant benefit over placebo or sham for abdominal pain or overall response.

Conclusion: CAM therapies such as herbal or dietary supplements and mind-body based approaches may be beneficial for abdominal pain and overall response in IBS. However, overall quality of evidence is low. Rigorous, high quality clinical trials are warranted to investigate CAM in IBS.

Keywords: dietary; herbal; body based; cognitive behavioral therapy; acupuncture; abdominal pain

WHAT YOU NEED TO KNOW

Background: Many patients with IBS, even those satisfied with traditional therapy, pursue complementary alternative medicine (CAM). It is important for clinicians to understand the evidence of these therapies when counseling patients.

Findings: In this systematic review and meta-analysis of randomized controlled trials, specific CAM therapies were beneficial for abdominal pain (herbal, mind-body) and overall response in IBS (herbal or dietary supplements, mind-body). However, the strength of the evidence is low.

Implications for care: It is important for clinicians to recognize that CAM could have a role for the management of IBS; however, high quality randomized clinical trials should be pursued to validate these observations.

INTRODUCTION

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder, with an estimated global prevalence of 5.8%-17.5%.[1] It is associated with significant healthcare and financial burden, as well as quality of life consequences. Patients and providers are often unsatisfied with available pharmacologic remedies and may seek complementary and alternative medicine (CAM),[2] a unique and holistic approach to treatment that is not a typical component of conventional medicine. CAM therapies are also sought out by patients who are satisfied with conventional therapy[3] and to supplement conventional treatment options[4]. It is important for physicians to understand the evidence behind CAM in order to appropriately counsel patients on their use. Studied CAM therapies include herbal remedies, dietary supplements, mind-body based interventions, body-based interventions, and energy-healing therapies. To clarify the clinical utility of CAM for management of IBS, critical assessment of the available evidence that exists on this topic is required.

Although several systematic reviews and meta-analyses on specific CAM therapies have been performed, outcome assessments have been limited and comparisons have generally been made to Western approaches, pharmacological therapies, wait-list controls or usual care which may contribute to uncertain estimates of efficacy. A previous systematic review investigating placebo response in CAM trials in IBS reported a pooled estimate of the placebo response rate to be 42.6%, demonstrating the importance of considering placebo effects and methodological rigor of clinical CAM trials in IBS[5]. Studies assessing specific CAM therapies include a recently published systematic review and network meta-analyses that found needle acupuncture plus Geshanxiaoyao formula and moxibustion to be associated with the highest probabilities of improving global IBS symptoms[6]. However, other patient-reported outcomes such as individual

symptoms (e.g. abdominal pain) were not assessed. Other carefully conducted reviews including network meta-analyses have reported benefit with psychological therapies in IBS, but the majority of included studies had no placebo or sham comparison leading to concerns for possible overestimation of treatment effects[7, 8]. Meanwhile, a 2016 systematic review and meta-analysis[9] of randomized controlled trials (RCTs) of Chinese herbal medicine for diarrhea-predominant IBS found significant improvement in overall symptoms, diarrhea, and abdominal pain, but was restricted by small patient numbers and a limited bias assessment.

Our aim was to conduct an updated and comprehensive systematic review and meta-analysis examining the efficacy of CAM therapies including herbal and dietary supplements, mind-body based intervention, body-based methods, and energy-based healing therapies vs. placebo or sham therapy for the clinical efficacy endpoints of abdominal pain and overall response in patients with IBS.

METHODS

A systematic review and meta-analysis was conducted in accordance with the PRISMA-P statement to provide detailed, transparent reporting[10]. The study protocol was published on PROSPERO (registration number CRD42018108040). Endnote X9 and Microsoft Excel were used to manage data.

Search strategy and study selection: A search of Ovid MEDLINE, Embase, and PsycINFO for randomized, placebo- or sham-controlled trials of CAM therapies in adults with IBS through June 2020 was conducted by a librarian (HC) and was adapted from the Scottish Intercollegiate Guidelines Network.[11] Bibliographies of relevant papers were reviewed. There were no language or date limitations. A list of search terms can be found in the Supplement.

RCTs comparing CAM to placebo or sham for abdominal pain and/or overall response in adults with IBS were eligible. Details on study eligibility criteria are included in the Supplemental Methods. CAM therapies included herbal and dietary supplements, mind-body based therapies, body-based therapies, and energy-based therapies. Two reviewers (WB and KM) independently reviewed titles and abstracts identify potentially relevant articles for full text review. Agreement was evaluated using the kappa statistic.[12] Both reviewers reviewed full text articles in detail. Disagreements were harmonized by consensus or by a third party when required (AS).

Study Outcomes: Primary outcomes were the effect of CAM-based therapy compared to placebo or sham on (1) mean improvement in abdominal pain (continuous variable), consistent with the Food and Drug Administration's (FDA) guidance on clinical endpoints for IBS trials,[13] and (2) efficacy according to overall response as defined by each study protocol (dichotomous variable). Frequency and types of adverse events were also analyzed.

Data Extraction: Data extraction was performed independently (WB and KM)**.** Clinical data extracted from each trial included study participant characteristics, interventions, control type, duration of therapy, and outcomes. For abdominal pain, data were extracted as mean change in abdominal pain severity. When mean improvement was not reported or could not be calculated, we extracted the mean or median values for post-treatment score.[14] Proxy scores for abdominal pain (e.g. overall symptom severity score) were used when not directly reported or provided by authors. For overall response, data were extracted as dichotomous outcomes, defined as the proportion of patients achieving the pre-specified study endpoint of response. Data were extracted as intention-to-treat analyses, using all available data for continuous outcomes and assuming drop-outs to be non-responders for dichotomous outcomes. Discrepancies were settled

by a third independent author (AS). For studies involving multiple treatment arms compared to one control arm, treatment arms were combined for an overall treatment effect when appropriate (i.e. when multiple doses of the same therapy were used). Authors of studies with incomplete data were contacted via email to obtain the necessary information.

Quality of evidence: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the methodological quality of included RCTs as well as the strength of the body of evidence.[15]

Data synthesis and statistical analysis: Meta-analytic estimates of treatment effect were expressed as standardized mean difference (SMD) for improvement in abdominal pain severity and relative risk (RR) for overall response. The random effects model was used due to known clinical and methodologic heterogeneity of studies (different CAM treatments). Heterogeneity was assessed using the Higgins and Thompson I^2 statistic and its associated confidence interval[16]. To investigate potential sources of heterogeneity, subgroup and meta-regression analyses were performed by intervention type, risk of bias, location, IBS definition, IBS type, IBS severity, proportion of female subjects and placebo response rates when possible. Publication bias was evaluated using funnel plots and Egger's test. When there was significant heterogeneity, a Baujat plot was used to detect of outliers.[17] Sensitivity analyses were performed after excluding these articles. Number needed to treat (NNT) values were calculated using the formula NNT (1/[control event rate×(1−RR)]). All analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing).[18] Statistical tests were 2-sided with a significance level of 0.05.

RESULTS

The literature search yielded 2825 distinct articles, of which 220 were retrieved for full text review. Agreement between authors was almost perfect (kappa statistic = 0.90). Of the 220 articles reviewed in detail, 66 articles comprising 6764 total participants were included (Figure 1) in the final analysis[19-84]. Three studies[31, 37, 38] examined more than one intervention compared to separate control arms and were included separately. Study characteristics are shown in Table 1. Risk of bias assessments are shown in Supplementary Table 1. GRADE assessments for each outcome and for each therapy class are included in Table 2. Results of subgroup analyses not shown in the main manuscript are included in Supplementary Table 2.

Efficacy of body-based therapy: Data on the efficacy of body-based therapy for abdominal pain were analyzed from 7 papers containing 8 RCTs evaluating 308 patients. There were no significant differences in abdominal pain between body-based therapy and placebo with low heterogeneity (SMD=-0.04, 95% CI: -0.36 to 0.28, I^2=12%, [Supplementary Figure 1]) and low confidence in estimates. All but one study[22] evaluated relaxation therapy. Excluding this study did not change results (SMD=-0.08, 95% CI: -0.45 to 0.29). There were no subgroup differences by risk of bias and no significant publication bias (p=0.46).

Data on efficacy of body-based therapy for overall response in IBS were available in 5 papers containing 6 RCTs evaluating 270 patients. Pooled analysis demonstrated no difference in overall response between body-based therapy and placebo with moderate heterogeneity (RR=1.32, 95% CI: 0.89 to 1.95, I^2=40%, [Supplementary Figure 2]) and low confidence in estimates. Three studies[31, 42, 72] were large contributors to heterogeneity and exclusion reduced heterogeneity (I^2=22%) without changing treatment effect (RR=1.49, 95% CI: 0.96 to 2.31). Exclusion of the only study[42] that did not use a relaxation intervention demonstrated similar

findings (RR=1.16, 95% CI: 0.76 to 1.78, I^2=4%). There were no subgroup differences by risk of bias and no significant publication bias (p=0.69).

Efficacy of dietary supplements: Data on the efficacy of dietary supplements for abdominal pain were analyzed from 15 papers containing 15 RCTs evaluating 939 patients. Pooled analysis demonstrated no significant difference between dietary supplements and placebo with considerable heterogeneity (SMD=0.13, 95% CI: -0.26 to 0.51, I^2=87%, [Supplementary Figure 3]) and low confidence in estimates. Exclusion of one outlier study[84] improved heterogeneity (I^2=59%) with no significant change in results (SMD=-0.02, 95% CI: -0.26 to 0.22). There were no subgroup differences by intervention type, risk of bias, location, IBS subtype, IBS severity or duration of therapy. Meta-regression, excluding the outlier study, demonstrated a negative association between percent females and treatment effect (p=0.02), but no association between placebo response and treatment effect (p=0.14). There was no significant publication bias (p=0.57).

Data on efficacy of dietary supplements for overall response in IBS were available in 7 papers containing 7 RCTs evaluating 432 patients. Dietary supplements were associated with benefit compared to placebo in overall response (RR=1.95, 95% CI: 1.02 to 3.73, I^2=75%, [Supplementary Figure 4]) corresponding to an NNT of 4 (95% CI: 2 to 189) with moderate heterogeneity and moderate confidence in estimates. Exclusion of two outliers[79, 84] reduced heterogeneity (I^2=0%) with minimal change in effect (RR=1.86, 95% CI: 1.39 to 2.48). There were no subgroup differences by intervention type or risk of bias (both p=ns) and no significant publication bias (p=0.37).

Efficacy of energy-healing therapy: Data on the efficacy of energy-healing therapy for abdominal pain were analyzed from 6 papers containing 6 RCTs evaluating 464 patients. Pooled analysis demonstrated no difference compared to placebo with moderate heterogeneity (SMD=0.21, 95% CI: -0.20 to 0.61, I^2=47%, [Supplementary Figure 5]) and low confidence in estimates. Exclusion of one outlier[21] reduced heterogeneity with no change in effect (SMD=0.12, 95% CI: -0.13 to 0.37, I^2=0%). There were no subgroup differences by intervention type or risk of bias (both p=ns) and no significant publication bias (p=0.60).

Data on efficacy of energy-healing for overall response in IBS were available in 3 papers containing 4 RCTs, all of which evaluated acupuncture, in 299 patients. Pooled analysis demonstrated no difference between energy-healing and placebo with low heterogeneity (RR=1.32, 95% CI: 0.99 to 1.76, I^2=0%, [Supplementary Figure 6]) and low confidence in estimates. There was no significant publication bias (p=0.67).

Efficacy of herbal therapies: Data on the efficacy of herbal therapies for abdominal pain were analyzed from 17 papers containing 17 RCTs evaluating 2248 patients. Pooled analysis demonstrated a significant effect with herbal therapies over placebo with considerable heterogeneity (SMD=0.47, 95% CI: 0.20 to 0.75, I^2=82%, [Figure 2]) and with low confidence. Two studies[63, 69] were outliers and exclusion increased treatment effect while reducing heterogeneity (SMD=0.61, 95% CI: 0.39 to 0.82, I^2=69%). There were no subgroup differences by intervention type, risk of bias, location, IBS definition, IBS type, or study duration. Meta-regression, excluding outliers, demonstrated no significant associations between treatment effect and percent females (p=0.34) or placebo response (p=0.99). There was no significant publication bias (p=0.97).

Data on efficacy of herbal therapies for overall response in IBS were available in 20 papers containing 20 RCTs evaluating 2833 patients. Herbal therapy was associated with benefit over placebo (RR=1.57, 95% CI: 1.31 to 1.88, I^2=77%, [Figure 4]), corresponding to an NNT of 5 (95% CI: 4 to 9) with high heterogeneity and moderate confidence in estimates. Three studies[36, 63, 69] were large contributors to heterogeneity and exclusion reduced heterogeneity without changing treatment effect (RR=1.68, 95% CI: 1.45 to 1.96, I^2=26%). There were no subgroup differences by intervention type, risk of bias, IBS definition, IBS type, or study location. Subgroup differences by location were observed ($p<0.01$), due to one study from North America.[69] On meta-regression there was no association between treatment effect and percent females (p=0.38), but overall response was negatively associated with placebo response rate ($p<0.01$). Two studies[63, 69] had a large impact on this association; after exclusion, the association was no longer significant (p=0.08). There was no significant publication bias (p=0.55).

Efficacy of mind-body based therapy: Data on the efficacy of mind-body based for abdominal pain were analyzed from 14 papers containing 14 RCTs evaluating 1618 patients. Pooled analysis demonstrated benefit with intervention over placebo of borderline significance with high heterogeneity (SMD=0.29, 95% CI: -0.01 to 0.59, I^2=78%, [Figure 3]) and very low confidence in estimates. Two studies[43, 49] were large contributors to heterogeneity; exclusion reduced heterogeneity and changed the treatment effect to be statistically significant (SMD=0.27, 95% CI: 0.0002 to 0.53, I^2=50%). There were no subgroup differences by intervention type, risk of bias, location, or study duration. There were subgroup differences by IBS definition ($p<0.01$, Supplementary Figure 7) and IBS severity with a larger treatment effect observed in non-severe IBS ($p\leq0.01$, Supplementary Figure 8). On meta-regression, there were no significant

associations between treatment effect and percent females (p=0.57) or placebo response (p=0.45). Egger's test showed asymmetry of the funnel plot (p=0.07) due to two studies.[37, 43]

Data on efficacy of mind-body based therapy for overall response in IBS were available in 12 papers containing 12 RCTs evaluating 1539 patients. Mind-body based therapy was associated with benefit over placebo (RR=1.67, 95% CI: 1.13 to 2.49, I^2=63%, [Supplementary Figure 9]),, corresponding to an NNT of 5 (95% CI: 3 to 25) with moderate heterogeneity and low confidence in estimates. Two studies[55, 62] were large contributors to heterogeneity and exclusion reduced heterogeneity without changing treatment effect (RR=1.62, 95% CI: 1.26 to 2.08, I^2=27%). There were no subgroup differences by intervention type, risk of bias, location, or IBS severity. On meta-regression, there was no significant association between treatment effect and percent females (p=0.78), but overall response was negatively associated with placebo response even after removing outliers (p<0.01). Egger's test showed asymmetry of the funnel plot (p=0.10) due to one study.[55]

Adverse events: Forty-three trials reported adverse events (AEs). AEs often overlapped with symptoms of IBS, particularly in dietary and herbal supplements. Headaches were commonly reported. Herbal studies that measured liver function chemistries did not report significant changes in laboratory parameters. Fourteen of 17 studies evaluating mind-body based therapies did not measure AEs; the few studies that did reported none. Energy-healing studies reported no AEs except for one study that reported mild musculoskeletal AEs. No studies reported serious AEs.

DISCUSSION

This updated systematic review and meta-analysis of randomized placebo or sham-controlled trials summarizes effects of CAM therapies on key patient-reported outcomes of abdominal pain and overall response and in IBS. Herbal and mind-body based therapies were the only CAM therapies for which there was evidence of benefit for abdominal pain. However, there was notable heterogeneity between studies even after excluding outliers. For mind-body based therapy, there was also evidence of publication bias or small study effects and subgroup analysis revealed differences by IBS severity with larger treatment effects in non-severe IBS. Pooled analysis of body-based therapy, energy-healing therapy and dietary supplements demonstrated no significant benefit for abdominal pain with variable degrees of heterogeneity.

For overall response, herbal, dietary and mind-body based therapies were associated with benefit over placebo or sham. There was no evidence of significant publication bias; however, moderate to high heterogeneity between studies was observed for all three therapies, which appeared to be driven by the presence of a few outliers. Among herbal therapy and mind-body based trials, meta-regression further revealed a negative association between treatment affect and placebo response, reaffirming the importance of measuring placebo responses when evaluating the efficacy of CAM in clinical IBS trials. Although a trend towards benefit with energy-healing therapy was observed, differences compared to placebo or sham were not statistically significant. There was no significant benefit with body-based therapies over placebo; however, moderate heterogeneity was noted that was not explained by subgroup analyses.

Prior reviews have also demonstrated a benefit with the mind-body based therapies, but these studies largely compared interventions to wait-list controls or usual care which may overestimate treatment responses.[8, 85] Our findings demonstrate that even when limiting analyses to studies designed with sham or placebo controls, mind-body therapies continue to demonstrate

evidence for efficacy for both abdominal pain and overall response with potential increased efficacy in patients with non-severe IBS.

Not all studies reported AEs, and many reported AEs overlapped with symptoms of IBS. No serious AEs were reported, suggesting that overall, CAM therapies demonstrate a reasonable safety profile in IBS.

Major aspects that differentiate this systematic review and meta-analysis from prior reviews is the comprehensive coverage summarizing available data on various CAM therapies from 66 articles involving 6764 patients, extensive subgroup and sensitivity analyses to identify potential contributors to inconsistency or heterogeneity, detailed examination of study quality, separate assessment of abdominal pain as a patient-reported outcome and our focus on placebo or sham controlled trials. The placebo effect is directly correlated with the expectation and experience that the placebo delivers. Prior meta-analyses for specific CAM therapies have had variable comparison groups that may not represent an optimal 'placebo' control. We applied strict criteria used to define an acceptable placebo or sham. Only studies with a control arm deemed to be an adequately comparable experience with comparable expectations to the intervention were included. Many previously published meta-analyses on IBS have used controls including wait-lists, no therapy, or different modalities of therapy.[8, 85] However, inadequate placebo controls may lead to a more favorable intervention response, particularly in an IBS patient population where high placebo responses are common. Additionally, our search strategy led to the inclusion of studies from around the world, which may make results more broadly generalizable. These aforementioned strengths enable a more thorough and informed assessment of the efficacy of available CAM therapies for IBS.

Our study does have some limitations. As expected, there was notable heterogeneity that

was not completely explained by subgroup analyses within each therapy type for either of the measured outcomes. However, in several cases, sensitivity analyses revealed sources of potential heterogeneity through the identification of outliers while subgroup analyses suggested differences due to patient characteristics and placebo response rates. Another limitation is some degree of reporting bias. Several potentially eligible studies were excluded as the data were unusable for our means or unavailable despite contacting the corresponding authors. Only a handful of studies were rated as low risk of bias in every area for abdominal pain and overall response, and overall confidence in estimates low to very low (Table 2 and Supplementary Table 1). In general, dietary and herbal therapies tended to be at lower risk of bias compared to other therapies, which is not unexpected given the relative ease of producing a comparable placebo and the feasibility of blinding participants. As reported by others,[86] there are inherent limitations in the methodological quality of individual studies of CAM therapy. Lastly, there was incomplete capturing of potentially important factors such as IBS severity, which was not reported in many studies, and whether or not CAM was utilized as an adjunct to conventional therapies or after failed conventional therapy.

Although the mechanisms by which CAM therapies confer benefit for symptoms of IBS are not fully understood, the CAM modalities covered in this study may target many of the mechanisms implicated in IBS pathophysiology including altered brain-gut connections, enteroendocrine abnormalities, altered motility, intestinal hypersensitivity and increased intestinal permeability.[87] Benefit with mind-body based interventions such as cognitive behavioral therapy and hypnotherapy may occur via the brain-gut axis[88] through targeting of psychological factors and central dysregulation critical to pain processing and perceptual responses. Mechanisms of action that have been proposed for acupuncture include pain

modulation and intestinal motility regulation;[56] however, no significant treatment effects were observed in this review. Herbal and dietary interventions may potentially exert benefit as observed in this study through effects on visceral hypersensitivity, intestinal permeability, and smooth muscle contractility.[19, 30, 33, 67, 84]

In conclusion, our findings add to the existing body of literature suggesting that mind-body based, herbal and dietary therapies exhibit some potential in IBS. There is a continued need for novel evidence-based practices for the optimal management of IBS, regardless of whether treatments are CAM or traditional Western medicine. Therapy options should also align with patients' willingness and preferences, who in many cases may be willing and interested in exploring CAM. CAM may also serve as a useful adjunct for patients who are refractory to traditional approaches. However, additional high quality RCTs are needed, particularly studies of adequate methodological rigor that have appropriately designed placebo or sham controls and validated, clinically meaningful endpoints. It would be beneficial for future studies to adopt the FDA's guidance on pharmaceutical treatments for IBS.[13] Further work on CAM in IBS should be pursued to maximize therapeutic options, increase CAM awareness among clinicians, and respond to patients' needs and experiences in IBS. It may be particularly worthwhile to focus future research efforts on herbal, dietary, and mind-body based therapies.

TABLE AND FIGURE LEGEND

Table 1: Study characteristics

Table 2: GRADE Summary

Figure 1: Study Selection

Figure 2: Forest plot of studies of herbal therapies vs. placebo or sham with effect on abdominal pain by intervention

Figure 3: Forest plot of studies of mind-body based therapy vs. placebo or sham with effect on abdominal pain by intervention

Figure 4: Forest plot of studies of herbal therapies vs. placebo or sham with effect on overall response by intervention

REFERENCES

1. Sperber AD, Dumitrascu D, Fukudo S, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies: a Rome Foundation working team literature review. Gut. 2017;66(6):1075-82. Epub 2016/01/29.

2. Wu JCY. Complementary and alternative medicine modalities for the treatment of irritable bowel syndrome: Facts or myths? Gastroenterology and Hepatology. 2010;6(11):705-11.

3. Van Tilburg MAL, Palsson OS, Levy RL, et al. Complementary and alternative medicine use and cost in functional bowel disorders: A six month prospective study in a large HMO. BMC Complementary and Alternative Medicine. 2008;8.

4. Lahner E, Bellentani S, Bastiani RD, et al. A survey of pharmacological and nonpharmacological treatment of functional gastrointestinal disorders. United European Gastroenterol J. 2013;1(5):385-93. Epub 2014/06/12.

5. Dorn SD, Kaptchuk TJ, Park JB, et al. A meta-analysis of the placebo response in complementary and alternative medicine trials of irritable bowel syndrome. Neurogastroenterol Motil. 2007;19(8):630-7. Epub 2007/07/21.

6. Wu IXY, Wong CHL, Ho RST, et al. Acupuncture and related therapies for treating irritable bowel syndrome: overview of systematic reviews and network meta-analysis. Therap Adv Gastroenterol. 2019;12:1756284818820438. Epub 2019/02/06.

7. Black CJ, Thakur ER, Houghton LA, et al. Efficacy of psychological therapies for irritable bowel syndrome: systematic review and network meta-analysis. Gut. 2020. Epub 2020/04/12.

8. Ford AC, Lacy BE, Harris LA, et al. Effect of Antidepressants and Psychological Therapies in Irritable Bowel Syndrome: An Updated Systematic Review and Meta-analysis. Am J Gastroenterol. 2018.

9. Zhu JJ, Liu S, Su XL, et al. Efficacy of Chinese Herbal Medicine for Diarrhea-Predominant Irritable Bowel Syndrome: A Meta-Analysis of Randomized, Double-Blind, Placebo-Controlled Trials. Evidence-based Complementary and Alternative Medicine. 2016;2016.

10. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015;4(1).

11. Scottish Intercollegiate Guidelines N. Search Filters: Randomised Controlled Trials. [Web Page]: Healthcare Improvement Scotland; 2019 [2019-01-07]; Available from: https://www.sign.ac.uk/search-filters.

12. Landis JR, Koch GG. An Application of Hierarchical Kapp-type Statistics in the Assessment of Majority Agreement among Multiple Observers. Biometrics. 1977;33:363-74.

13. Research FaDACfDEa. Guidance for Industry Irritable Bowel Syndrome. Clinical Evaluation of Drugs for Treatment: U.S. Department of Health and Human Services; 2012.

14. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the saple size, median, range, and/or interquartile range. BMC Medical Research Methodology. 2014;14(135).

15. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928. Epub 2011/10/20.

16. Higgins JPT, S.G. T, Deeks JJ. Measuring inconsistency in meta-analysis. Bmj. 2003;327:557-60.

17. Baujat B, Mahe C, Pignon JP, et al. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. Stat Med. 2002;21(18):2641-52. Epub 2002/09/14.

18. Team RC. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.

19. Acosta A, Camilleri M, Linker-Nord S, et al. A pilot study of the effect of daikenchuto on rectal sensation in patients with irritable bowel syndrome. Journal of Neurogastroenterology and Motility. 2016;22(1):69-77.

20. Alt F, Chong PW, Teng E, et al. Evaluation of Benefit and Tolerability of IQP-CL-101 (Xanthofen) in the Symptomatic Improvement of Irritable Bowel Syndrome: A Double-Blinded, Randomised, Placebo-Controlled Clinical Trial.[Erratum appears in Phytother Res. 2018 Mar;32(3):564; PMID: 29508485]. Phytother Res. 2017;31(7):1056-62.

21. Anastasi JK, McMahon DJ, Kim GH. Symptom management for irritable bowel syndrome: a pilot randomized controlled trial of acupuncture/moxibustion. Gastroenterol Nurs. 2009;32(4):243-55.

22. Attali TV, Bouchoucha M, Benamouzig R. Treatment of refractory irritable bowel syndrome with visceral osteopathy: short-term and long-term results of a randomized trial. J Dig Dis. 2013;14(12):654-61.

23. Azpiroz F, Dubray C, Bernalier-Donadille A, et al. Effects of scFOS on the composition of fecal microbiota and anxiety in patients with irritable bowel syndrome: a randomized, double blind, placebo controlled study. Neurogastroenterol Motil. 2017;29(2).

24. Bensoussan A, Kellow JE, Bourchier SJ, et al. Efficacy of a Chinese Herbal Medicine in Providing Adequate Relief of Constipation-predominant Irritable Bowel Syndrome: A Randomized Controlled Trial. Clin Gastroenterol Hepatol. 2015;13(11):1946-54.e1.

25. Bensoussan A, Talley NJ, Hing M, et al. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. Jama. 1998;280(18):1585-9.

26. Blanchard EB, Lackner JM, Sanders K, et al. A controlled evaluation of group cognitive therapy in the treatment of irritable bowel syndrome. Behav Res Ther. 2007;45(4):633-48.

27. Blanchard EB, Schwarz SP, Suls JM, et al. Two controlled evaluations of multicomponent psychological treatment of irritable bowel syndrome. Behav Res Ther. 1992;30(2):175-89.

28. Brinkhaus B, Hentschel C, Von Keudell C, et al. Herbal medicine with curcuma and fumitory in the treatment of irritable bowel syndrome: a randomized, placebo-controlled, double-blind clinical trial. Scand J Gastroenterol. 2005;40(8):936-43.

29. Chen C, Tao C, Liu Z, et al. A Randomized Clinical Trial of Berberine Hydrochloride in Patients with Diarrhea-Predominant Irritable Bowel Syndrome. Phytother Res. 2015;29(11):1822-7.

30. Chen M, Tang TC, Wang Y, et al. Randomised clinical trial: Tong-Xie-Yao-Fang granules versus placebo for patients with diarrhoea-predominant irritable bowel syndrome. Alimentary Pharmacology and Therapeutics. 2018;48(2):160-8.

31. Craske MG, Wolitzky-Taylor KB, Labus J, et al. A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. Behav Res Ther. 2011;49(6-7):413-21.

32. Cremon C, Stanghellini V, Barbaro MR, et al. Randomised clinical trial: the analgesic properties of dietary supplementation with palmitoylethanolamide and polydatin in irritable bowel syndrome. Aliment Pharmacol Ther. 2017;45(7):909-22.

33. Dale HF, Jensen C, Hausken T, et al. Effects of a Cod Protein Hydrolysate Supplement on Symptoms, Gut Integrity Markers and Fecal Fermentation in Patients with Irritable Bowel Syndrome. Nutrients. 2019;11(7).

34. Davis K, Philpott S, Kumar D, et al. Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome. Int J Clin Pract. 2006;60(9):1080-6.

35. Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. Gastroenterology. 2003;125(1):19-31.

36. Fan H, Zheng L, Lai Y, et al. Tongxie Formula Reduces Symptoms of Irritable Bowel Syndrome. Clin Gastroenterol Hepatol. 2017;15(11):1724-32.

37. Fernández C, Amigo I. Efficacy of training in stress and contingency management in cases of irritable bowel syndrome. Stress and Health. 2006;22(5):285-95.

38. Fernandez C, Ferez M, Amigo I, et al. Stress and contingency management in the treatment of irritable bowel syndrome. Stress Medicine. 1998;14(1):31-42.

39. Flik CE, Laan W, Zuithoff NPA, et al. Efficacy of individual and group hypnotherapy in irritable bowel syndrome (IMAGINE): a multicentre randomised controlled trial. The Lancet Gastroenterology and Hepatology. 2019;4(1):20-31.

40. Forbes A, Jackson S, Walter C, et al. Acupuncture for irritable bowel syndrome: a blinded placebo-controlled trial. World J Gastroenterol. 2005;11(26):4040-4.

41. Gaylord SA, Palsson OS, Garland EL, et al. Mindfulness training reduces the severity of irritable bowel syndrome in women: results of a randomized controlled trial. Am J Gastroenterol. 2011;106(9):1678-88.

42. Grosjean D, Benini P, Carayon P. Managing irritable bowel syndrome: The impact of micro-physiotherapy. J Complement Integr Med. 2017;14(2):16.

43. Hunt MG, Moshier S, Milonova M. Brief cognitive-behavioral internet therapy for irritable bowel syndrome. Behav Res Ther. 2009;47(9):797-802.

44. Hutchings HA, Wareham K, Baxter JN, et al. A randomised, cross-over, placebo-controlled study of aloe vera in patients with irritable bowel syndrome: Effects on patient quality of life. ISRN Gastroenterology. 2011;2011.

45. Jang AL, Hwang SK, Kim DU. The effects of cognitive behavioral therapy in female nursing students with irritable bowel syndrome: a randomized trial. Eur J Gastroenterol Hepatol. 2014;26(8):918-26.

46. Kamiya T, Shikano M, Tanaka M, et al. Therapeutic effects of biobran, modified arabinoxylan rice bran, in improving symptoms of diarrhea predominant or mixed type irritable bowel syndrome: A pilot, randomized controlled study. Evidence-based Complementary and Alternative Medicine. 2014;2014.

47. Kazemian A, Toghiani A, Shafiei K, et al. Evaluating the efficacy of mixture of Boswellia carterii, Zingiber officinale, and Achillea millefolium on severity of symptoms, anxiety, and depression in irritable bowel syndrome patients. Journal of Research in Medical Sciences. 2017;22(11).

48. Ko SJ, Han G, Kim SK, et al. Effect of Korean herbal medicine combined with a probiotic mixture on diarrhea-dominant irritable bowel syndrome: A double-blind, randomized, placebo-controlled trial. Evidence-based Complementary and Alternative Medicine. 2013;2013.

49. Lackner JM, Jaccard J, Keefer L, et al. Improvement in Gastrointestinal Symptoms After Cognitive Behavior Therapy for Refractory Irritable Bowel Syndrome. Gastroenterology. 2018;155(1):47-57.

50. Lahmann C, Rohricht F, Sauer N, et al. Functional relaxation as complementary therapy in irritable bowel syndrome: a randomized, controlled clinical trial. J Altern Complement Med. 2010;16(1):47-52.

51. Lee J-H, Kim JI, Baeg MK, et al. Effect of Samryungbaekchul-san Combined with Otilonium Bromide on Diarrhea-Predominant Irritable Bowel Syndrome: A Pilot Randomized Controlled Trial. Journal of clinical medicine. 2019;8(10).

52. Lembo AJ, Conboy L, Kelley JM, et al. A treatment trial of acupuncture in IBS patients. Am J Gastroenterol. 2009;104(6):1489-97.

53. Leung WK, Wu JC, Liang SM, et al. Treatment of diarrhea-predominant irritable bowel syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled trial. Am J Gastroenterol. 2006;101(7):1574-80.

54. Lindfors P, Unge P, Arvidsson P, et al. Effects of gut-directed hypnotherapy on IBS in different clinical settingsresults from two randomized, controlled trials. Am J Gastroenterol. 2012;107(2):276-85.

55. Ljótsson B, Falk L, Vesterlund AW, et al. Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome - A randomized controlled trial. Behaviour Research and Therapy. 2010;48(6):531-9.

56. Lowe C, Aiken A, Day AG, et al. Sham acupuncture is as efficacious as true acupuncture for the treatment of IBS: A randomized placebo controlled trial. Neurogastroenterol Motil. 2017;29(7).

57. Ma YX, Liu X, Liu CZ, et al. Randomized clinical trial: The clinical effects of herb-partitioned moxibustion in patients with diarrhoea-predominant irritable bowel syndrome. Evidence-based Complementary and Alternative Medicine. 2013;2013.

58. Madisch A, Holtmann G, Plein K, et al. Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial. Aliment Pharmacol Ther. 2004;19(3):271-9.

59. Mak AD-P, Chung VCH, Yuen SY, et al. Noneffectiveness of electroacupuncture for comorbid generalized anxiety disorder and irritable bowel syndrome. Journal of gastroenterology and hepatology. 2019;34(10):1736-42.

60. Merat S, Khalili S, Mostajabi P, et al. The effect of enteric-coated, delayed-release peppermint oil on irritable bowel syndrome. Dig Dis Sci. 2010;55(5):1385-90.

61. Mosaffa-Jahromi M, Lankarani KB, Pasalar M, et al. Efficacy and safety of enteric coated capsules of anise oil to treat irritable bowel syndrome. J Ethnopharmacol. 2016;194:937-46.

62. Moser G, Tragner S, Gajowniczek EE, et al. Long-term success of GUT-directed group hypnosis for patients with refractory irritable bowel syndrome: a randomized controlled trial. Am J Gastroenterol. 2013;108(4):602-9.

63. Pan F, Zhang T, Zhang YH, et al. Effect of Tongxie Yaofang Granule in treating diarrhea-predominate irritable bowel syndrome. Chin J Integr Med. 2009;15(3):216-9.

64. Park HJ, Cha C. The effect of Korean hand acupuncture on young, single Korean students with irritable bowel syndrome. Gastroenterol Nurs. 2012;35(6):403-14.

65. Payne A, Blanchard EB. A controlled comparison of cognitive therapy and self-help support groups in the treatment of irritable bowel syndrome. J Consult Clin Psychol. 1995;63(5):779-86.

66. Peckham EJ, Relton C, Raw J, et al. Interim results of a randomised controlled trial of homeopathic treatment for irritable bowel syndrome. Homeopathy. 2014;103(3):172-7.

67. Portincasa P, Bonfrate L, Scribano ML, et al. Curcumin and Fennel Essential Oil Improve Symptoms and Quality of Life in Patients with Irritable Bowel Syndrome. J. 2016;25(2):151-7.

68. Saha L, Malhotra S, Rana S, et al. A preliminary study of melatonin in irritable bowel syndrome. J Clin Gastroenterol. 2007;41(1):29-32.

69. Saito YA, Rey E, Almazar-Elder AE, et al. A randomized, double-blind, placebo-controlled trial of St John's wort for treating irritable bowel syndrome. Am J Gastroenterol. 2010;105(1):170-7.

70. Sallon S, Ben-Arye E, Davidson R, et al. A novel treatment for constipation-predominant irritable bowel syndrome using Padma Lax, a Tibetan herbal formula. Digestion. 2002;65(3):161-71.

71. Shin DW, Yoon H, Kim HS, et al. Effects of Alkaline-Reduced Drinking Water on Irritable Bowel Syndrome with Diarrhea: A Randomized Double-Blind, Placebo-Controlled Pilot Study. Evidence-based Complementary and Alternative Medicine. 2018;2018.

72. Shinozaki M, Kanazawa M, Kano M, et al. Effect of autogenic training on general improvement in patients with irritable bowel syndrome: a randomized controlled trial. Appl Psychophysiol Biofeed. 2010;35(3):189-98.

73. Simren M, Ringstrom G, Bjornsson ES, et al. Treatment with hypnotherapy reduces the sensory and motor component of the gastrocolonic response in irritable bowel syndrome. Psychosom Med. 2004;66(2):233-8.

74. Størsrud S, Pontén I, Simrén M. A pilot study of the effect of aloe barbadensis mill. Extract (AVH200®) in patients with irritable bowel syndrome: A randomized, double-blind, placebo-controlled study. Journal of Gastrointestinal and Liver Diseases. 2015;24(3):275-80.

75. Su X, Tang Y, Zhang J, et al. Curative effect of warming kidney and fortifying spleen recipe on diarrhea-predominant irritable bowel syndrome. J Tradit Chin Med. 2013;33(5):615-9.

76. Tang XD, Lu B, Li ZH, et al. Therapeutic Effect of Chang'an I Recipe (I) on Irritable Bowel Syndrome with Diarrhea: A Multicenter Randomized Double-Blind Placebo-Controlled Clinical Trial. Chin J Integr Med. 2018;24(9):645-52.

77. Tkachuk GA, Graff LA, Martin GL, et al. Randomized controlled trial of cognitive-behavioral group therapy for irritable bowel syndrome in a medical setting. Journal of Clinical Psychology in Medical Settings. 2003;10(1):57-69.

78. Trifan A, Burta O, Tiuca N, et al. Efficacy and safety of Gelsectan for diarrhoea-predominant irritable bowel syndrome: A randomised, crossover clinical trial. United European gastroenterology journal. 2019;7(8):1093-101.

79. van Tilburg MA, Palsson OS, Ringel Y, et al. Is ginger effective for the treatment of irritable bowel syndrome? A double blind randomized controlled pilot trial. Complement Ther Med. 2014;22(1):17-20.

80. Vejdani R, Shalmani HR, Mir-Fattahi M, et al. The efficacy of an herbal medicine, Carmint, on the relief of abdominal pain and bloating in patients with irritable bowel syndrome: a pilot study. Dig Dis Sci. 2006;51(8):1501-7.

81. Wang G, Li TQ, Wang L, et al. Tong-xie-ning, a Chinese herbal formula, in treatment of diarrhea-predominant irritable bowel syndrome: a prospective, randomized, double-blind, placebo-controlled trial. Chin Med J. 2006;119(24):2114-9.

82. Wilson D, Evans M, Weaver E, et al. Evaluation of serum-derived bovine immunoglobulin protein isolate in subjects with diarrhea-predominant irritable bowel syndrome. Clinical Medicine Insights: Gastroenterology. 2013;6:49-60.

83. Yadav SK, Jain AK, Tripathi SN, et al. Irritable bowel syndrome: therapeutic evaluation of indigenous drugs. Indian J Med Res. 1989;90:496-503.

84. Zhou Q, Verne ML, Fields JZ, et al. Randomised placebo-controlled trial of dietary glutamine supplements for postinfectious irritable bowel syndrome. Gut. 2019;68(6):996-1002.

85. Manheimer E, Wieland LS, Cheng K, et al. Acupuncture for irritable bowel syndrome: systematic review and meta-analysis. Am J Gastroenterol. 2012;107(6):835-47; quiz 48. Epub 2012/04/11.

86. Koretz RL, Rotblatt M. Complementary and alternative medicine in gastroenterology: the good, the bad, and the ugly. Clin Gastroenterol Hepatol. 2004;2(11):957-67.

87. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. N Engl J Med. 2017;376(26):2566-78.

88. Simren M. Hypnosis for irritable bowel syndrome: the quest for the mechanism of action. Int J Clin Exp Hypn. 2006;54(1):65-84. Epub 2005/12/01.

Table 1: Study Characteristics

Study ID	Location	Outcome		Intervention	Control	IBS Details			Mean Age (SD)		% Female		Duration	N
		AP	OR			Definition	Type	Severity	CAM	Placebo	CAM	Placebo		
Body-Based														
Relaxation														9 studies
Blanchard 1992 - Study 1	USA	Likert	CPSR	PMR, thermal biofeedback, stress management	attention placebo	S	-	-	43.3	43	90	60	8 weeks	20
Blanchard 1992 - Study 2	USA	Likert	CPSR	PMR, thermal biofeedback, stress management	attention placebo	S	Any	-	43.9 (13.1)	43,9 (13.6)	65.6	66.7	8 weeks	61
Craske 2011 - Relaxation	USA	BSS	BSS	PMR, stress management	attention placebo	II	Any	-	39.47 (13.5)		74.3		10 weeks	63
Fernandez 1998 - Relaxation	Spain	Likert	Other	PMR, stress management	attention placebo	Manning	Any	PP	47	49	66	66	10 weeks	44
Fernandez 2006 - Relaxation	Spain	Likert	x	PMR, stress management	attention placebo	S	-	-	48.1 (10.1)		70		6 weeks	10
Lahmann 2010	Germany	Likert	x	functional relaxation	EMC + counseling	II	Any	-	49.7 (10.6)	47.9 (11.9)	72.5	60	5 weeks	80
Shinozaki 2010	Japan	Other	AR	autogenic training	diet discussions	II	Any	Refr	32.8 (2.8)	30.3 (15.4)	54.5	50	8 weeks	21
Other														
Attali 2013	France	VAS	x	visceral osteopathy	placebo manipulation	III	Any	Refr	50 (2)		74.2		4 weeks	31
Grosjean 2017	France	x	Other	micro-physiotherapy	sham therapy	S	-	-	51.5 (14.4)	55.6 (16.2)	64.5	60	4 weeks	61
Dietary Supplement														
Aloe Vera														15 studies
Davis 2006	England	IBS-SSS		aloe vera	placebo	II	Any	Refr	-	-	74	81	4 weeks	58
Hutchings 2001	England	GSRS	x	aloe vera	placebo	II	Any	Refr	46.0 (13.6)	47 (13.7)	76.4	76.4	5 months	110
Storsrud 2015	Sweden	IBS-SSS		aloe vera	placebo	III	-	-	43.9 (13.3)	44.2 (14.5)	72	77	4 weeks	68
Other														
Azpiroz 2017	Spain, France	Other	x	scFOS	placebo	III	Any	-	41.0 (11.1)	42.4 (10.6)	78	74	4 weeks	77
Chen 2015	China	IBS-SSS	x	berberine hcl	placebo	III	D	-	37.4	36.1	72.9	69.4	8 weeks	132
Cremon 2017	Italy	Likert	x	palmitoylethanolamide and polydatin	placebo	III	Any	-	37 (10.8)	40.4 (9.8)	62.1	44	12 weeks	54
Dale 2019	Norway	IBS-SSS	x	cod protein hydrolysate	placebo	IV	D, M	-	42.7 (11.9)	45.1 (14.8)	92	73	6 weeks	31
Kamiya 2014	Japan	GSRS		biobran	placebo	III	D, M	-	48.8 (14.7)	49.6 (16.0)	52.6	45	4 weeks	39
Mosaffa-Jahromi 2016	Iran	VAS	Other	enteric coated anise oil	placebo	III	Any	-	*34.6 (9.7)	32.4 (7.2)	51.3	45	4 weeks	120
Saha 2007	India	other	x	melatonin	placebo	II	-	Refr	[27]	[22]	33.3	33.3	8 weeks	18
Shin 2018	Korea	Likert	Other	alkaline water	placebo	III	D	-	43.3 (14.4)	40.1 (15.7)	76.9	71.4	8 weeks	27
Trifan 2019	Romania	Likert	x	XG+PPT+XOS	placebo	III	D	-	35.0 (7.8)	34.5 (8.1)	83	63	4 weeks	60
Van Tilburg 2014	USA	IBS-SSS	AR	ginger	placebo	III	-	-	-	-	-	-	4 weeks	45
Wilson 2013	Canada	Other	x	bovine IVG	placebo	II	D	-	*46.9 (9.7)	47.8 (10.4)	58.1	71.4	6 weeks	45
Zhou 2019	USA	IBS-SSS		oral glutamine	placebo	III	D	-	32.4 (9.5)	30.9 (7.1)	68.5	71.2	8 weeks	115
Energy-healing														
Acupuncture														8 studies
Anastasi 2009	USA	Likert	x	acupuncture and moxibustion	sham therapy	II	-	-	47.1	34.3	64.3	66.7	4 weeks	29
Forbes 2005	England	Likert	Improve	acupuncture	sham therapy	I, Manning	Any	-	43	44.4	59.3	71.9	12 weeks	59
Lembo 2009 - Augmented	USA	x	AR	acupuncture augmented interaction	sham therapy	II	Any	-	37.5 (14.6)	38.9 (14.1)	78	77	3 weeks	82
Lembo 2009 - Limited	USA	x	AR	acupuncture limited interaction	sham therapy	II	Any	-	37.5 (14.6)	38.9 (14.1)	78	77	3 weeks	71
Lowe 2017	Canada	McGill	Other	acupuncture	sham therapy	I	Any	-	42 (15)	43 (15)	84	72	4 weeks	87
Park 2012	Korea	BSS	x	korean hand acupuncture	sham therapy	III	Any	-	22.3 (3.2)	21.5 (2.7)	100	100	4 weeks	59
Other														
Ma 2013	China	GSRS	x	moxibustion	placebo moxibustion	III	D	-	26.7	25.4	77.3	76	4 weeks	150
Mak 2019	China	Likert	x	electroacupuncture	sham therapy	III	D	-	50.85 (11.57)	50.83 (14.15)	50	55	10 weeks	80
Herbal														
Curcuma														23 studies
Alt 2017	Malaysia	IBS-SSS	Improve	curcuma, peppermint oil, caraway oil	placebo	III	-	-	44 (13)	47.5 (14.8)	70	68.1	8 weeks	90
Brinkhaus 2005	Germany	VAS	Improve	curcuma, furmitory	placebo	S	Any	-	*49.3 (12.0)	47.2 (11.7)	64.6	62	18 weeks	119
Portincasa 2016	Italy	IBS-SSS	Improve	curcuma, fennel	placebo	III	Any	Mod	41.5	39.4	41	70.7	30 days	121

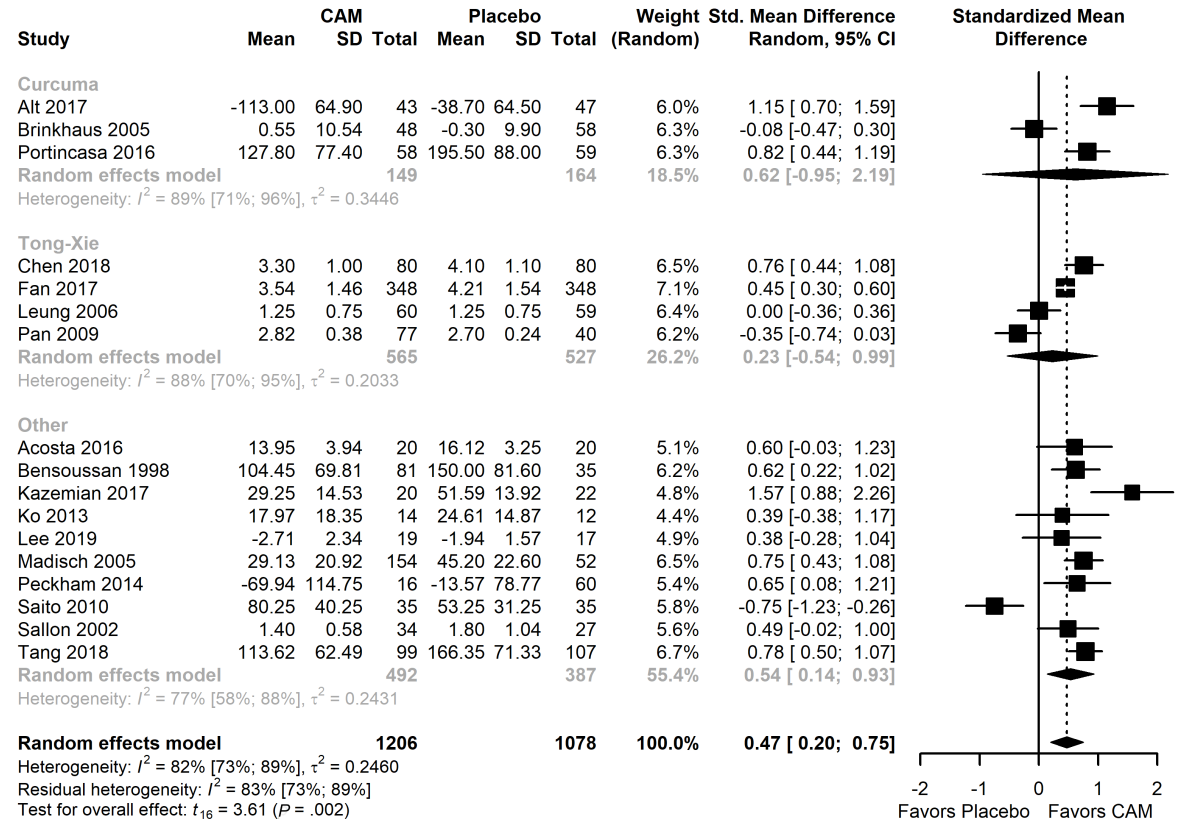
Tong-Xie															
Chen 2018	China	VAS	AR	tong-xie-yao-fang	placebo	III	D	-	35.4 (10.7)	32.7 (8.2)	48.8	61.3	3 weeks	160
Fan 2017	China	Likert	AR	tong-xie	placebo	III	D	-	36.3 (0.7)	36.6 (0.7)	58	59	4 weeks	696
Leung 2006	Wales	Likert	AR	tong-xie-yao-fang	placebo	II	D	-	45.4 (11.9)	43.6 (13.9)	48.3	55.9	8 weeks	119
Pan 2009	China	Likert	Nimodipine	tong-xie-yao-fang	placebo	III	D	-	39.2 (13.4)	37.5 (15.6)	58.8	57.5	4 weeks	120
Wang 2006	China	x	Other	tong-xie-ning	placebo	II	D	-	37.1 (10.4)	36.9 (8.9)	44.8	64.3	3 weeks	60
Other															
Acosta 2016	USA	VAS	x	diakenchuto	placebo	III	Any	-	39.5 (2.7)	43 (2.6)	100	100	2 weeks	40
Bensoussan 1998	Australia	BSS		chinese herbal medicine	placebo	I	Any	-	*47.5 (14.2)	45 (13.9)	68.6	63	16 weeks	116
Bensoussan 2015	Australia	x	AR	chinese herbal medicine	placebo	III	C	-	48.2 (1.25)	48.9 (1.5)	93.4	92.2	16 weeks	125
Kazemian 2017	Iran	IBS-SSS	x	boswellia caterii	placebo	III	Any	Mild-Mod	36.3 (10.9)	41.3 (12.6)	44.6	27.2	12 weeks	42
Ko 2013	Korea	VAS	AR	korean herbal medicine plus probiotic	placebo	III	D	-	47.5 (13.6)	47.5 (16.0)	37.5	23.5	8 weeks	26
Lee 2019	Korea	Likert	Improve	samryungbaekchul-san	placebo	III	D	-	38.05 (15.27)	45.2 (13.56)	20	45	8 weeks	36
Madisch 2005	Germany	VAS	Other	BCT and STW	placebo	S	Any	-	*46.4 (12.1)	46.1 (10.4)	63.1	57.7	4 weeks	208
Merat 2010	Iran	x	Other	peppermint oil	placebo	II	Any	-	35 (13)	37 (11)	84.8	63	8 weeks	90
Peckham 2014	England	IBS-SSS	x	homeopathic treatment	supportive listening	III	-	Mild	48.2 (13.5)	42.5 (16.2)	100	78	26 weeks	76
Saito 2010	USA	BSS	AR	st john wort	placebo	II	Any	-	[43]	[42]	86	86	12 weeks	70
Sallon 2002	Isreal	Likert	Other	padma lax	placebo	I	C	-	47.9 (2.1)	46.3 (2.9)	71	74	12 weeks	80
Su 2013	China	x	Nimodipine	sishen wen	placebo	III	D	-	38 (12)	37 (12)	55.8	59.2	4 weeks	240
Tang 2018	China	IBS-SSS	AR	chang' an I recipie	placebo	III	D	Any	42.9 (13.8)	42.5 (14.0)	37.4	38.3	8 weeks	216
Vejdani 2006	Iran	x	Other	carmint	placebo	II	Any	-	31 (10.8)	46 (12)	35.7	50	8 weeks	32
Yadav 1989	India	x	Other	ayurvedic herbal compound	placebo	S	Any	-	29.2	27.7	12.3	11.5	6 weeks	109
Mind-Body Based															
CBT															16 studies
Blanchard 2007	USA	McGill	x	group CBT	psychodeducational support	II	Any	Mod-Sev	48.1 (13.7)	51.5 (11.3)	77.1	92.5	2 weeks	82
Craske 2011 - CBT	USA	BSS		CBT with interoceptive exposure	attention placebo	II	Any	-	39.47 (13.5)		74.3		10 weeks	69
Drossman 2003	USA, Canada	McGill	Other	CBT	attention, education	I	Any	Mod-Sev	37.9 (11.8)	36.1 (11.8)	100	100	12 weeks	215
Hunt 2009	USA	GSRS	x	CBT	attention placebo	SI	-	-	39 (10)	38 (12)	76	85	6 weeks	54
Jang 2014	Korea	BSS	x	CBT	education, attention placebo	III	Any	-	21.9 (1.9)	21.2 (2.3)	100	100	8 weeks	81
Lackner 2018	USA	IBS-SSS	Other	CBT	education, group discussion	III	Any	Mod-Sev	*41.0 (14.5)	42.2 (15.4)	81.1	79.2	10 weeks	436
Ljotsson 2010	Sweden	Likert	CPSR	CBT	online support group	III	Any	-	36.4 (10.1)	32.8 (8.6)	83.3	86	10 weeks	86
Payne 1995	USA	x	CPSR	CBT	self-help support group	I	Any	-	39.7 (13.1)	44 (9.3)	83.3	91.7	8 weeks	24
Tkachuk 2003	Canada	Other	CPSR	group CBT	telephone attention control	I	Any	-	39.5		96		9 weeks	28
Hypnotherapy															
Filk 2019	Netherlands	IBS-SSS	AR	hypnotherapy	supportive educational therapy	III	-	-	37.3 (13.2)	34.5 (12.5)	77	89	12 weeks	342
Lindfors 2012 - Study 1	Sweden	Likert	Improve	gut-directed hypnotherapy	supportive listening	II	Any	Refr	43	41	77.8	80	12 weeks	90
Moser 2013	Austria	x	Other	gut-directed hypnotherapy	supportive listening	III	Any	Refr	40.4 (14.7)	50.8 (13.9)	80.4	78.7	12 weeks	100
Simren 2004	Sweden	Other	Other	gut-directed hypnotherapy	supportive listening	II	Any	Refr	42.4 (13.9)	41.5 (3.8)	64.3	71.4	12 weeks	28
Other															
Fernandez 1998 - Behavior	Spain	Likert	Other	contingency management	attention placebo	Manning	Any	PP	40	49	75	66	10 weeks	46
Fernandez 2006 - Behavior	Spain	Likert	x	contingency management	attention placebo	-	-	-	48.1 (10.1)		70		6 weeks	10
Gaylord 2011	USA	IBS-SSS		mindfullness	support group, education	II	-	-	44.7 (12.6)	40.9 (14.7)	100	100	8 weeks	75

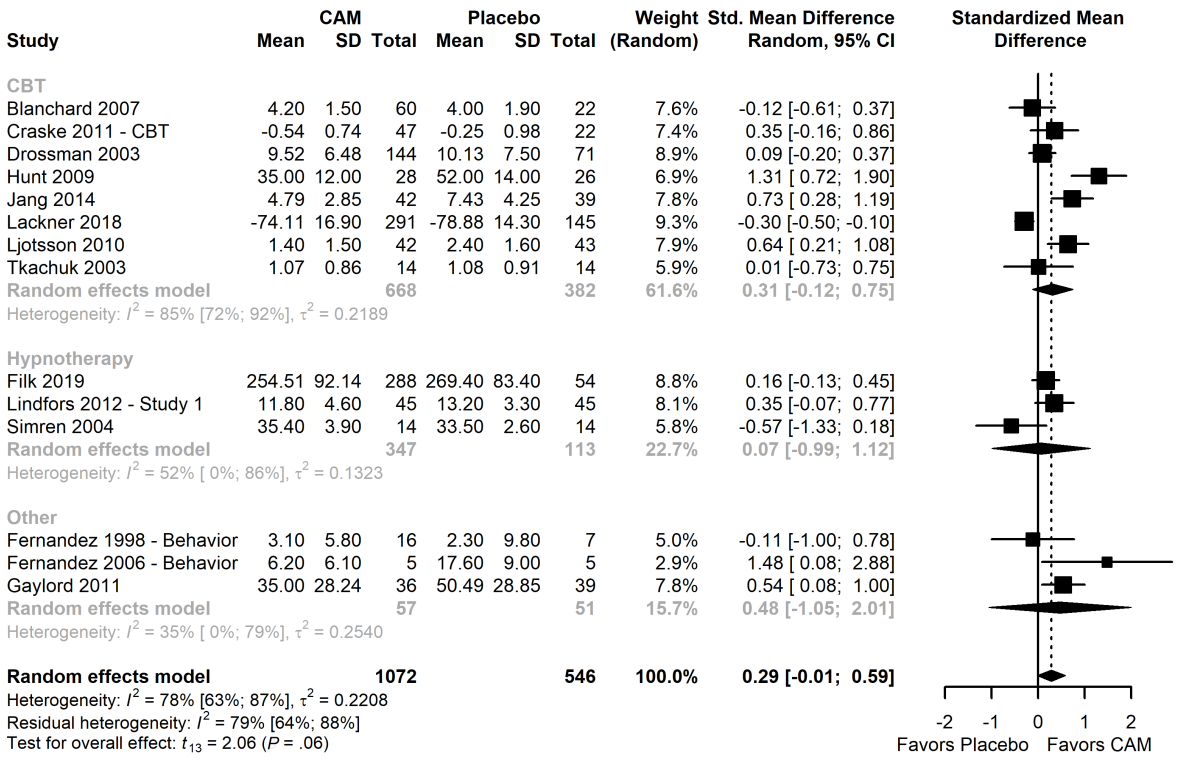
Note: USA = United States, AP = abdominal pain, OR = overall response, x = not studied, BSS = Bowel Symptom Score, IBS-SSS = IBS Symptom Severity Score, CPSR = Composite Primary Symptoms Reduction score, AR = adequate relief, VAS = Visual Analog Scale, GSRS = Gastrointestinal Symptom Rating Scale, CBT = cognitive behavioral therapy, scFOS = short-cahin fructooligosaccharides, PMR = progressive muscle relaxation, XG+PPT+XOS = xyloglucan, pea protein, tannins from grapeseed, xylo-oligosaccharides, BCT = bitter candyfruit, STW = iberogast, IVG = intravenous globin, - = not specified by article, * = combined mean (standard deviation) from multiple interventions, ** = mean age and standard deviation not reported, numbers listed in age groups, S = symptoms without organic disease, II = Rome II Criteria, III = Rome III Criteria, IV = Rome IV Criteria, SI = patient self-identified, Mod = moderate, Sev = severe, Refr = refractory, PP = poor prognosis, [#] = median age

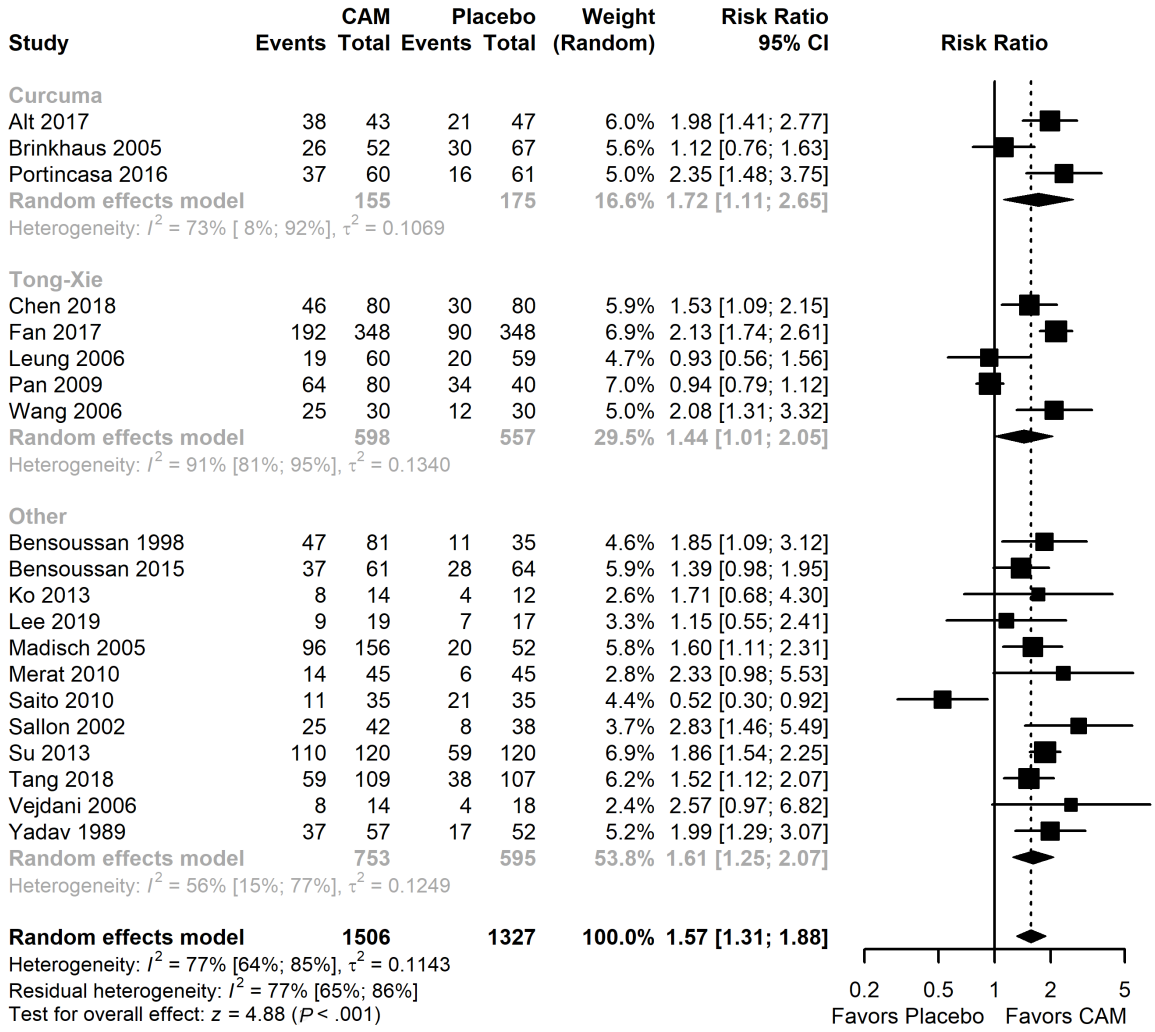
Table 2. Quality Assessment (GRADE) by Outcome

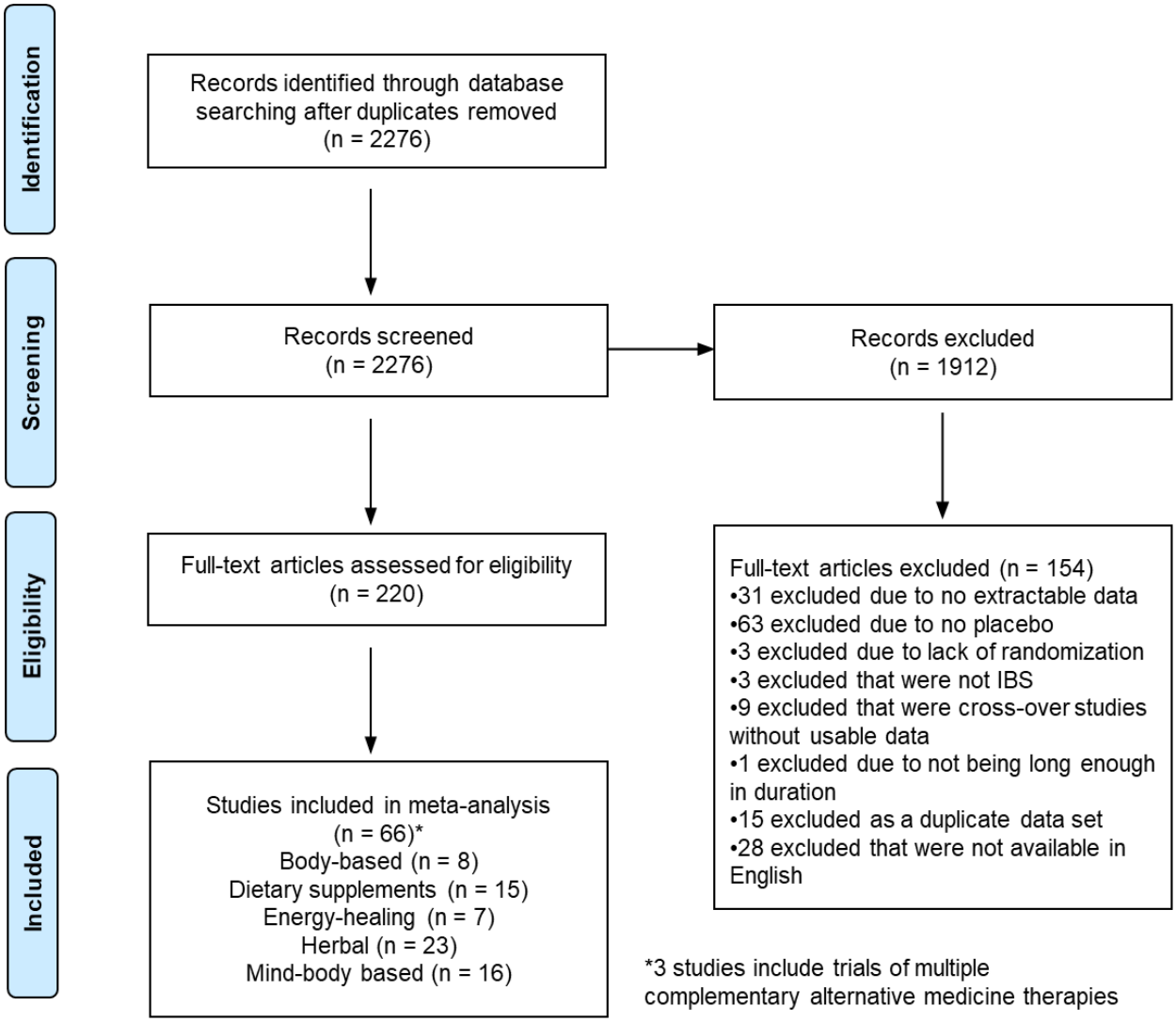
	Articles	RCTs	Intervention	CAM	Placebo	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality	Effect Estimate (95% CI)	
Abdominal Pain	**55**	**67**		**n=3175**	**n=2438**						**Very Low**	**SMD**	
	7	8	Body-Based	168	140	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	-0.04 (-0.36-0.28)	
	15	15	Dietary Supplements	497	442	Ser.	Ser.	Ser.	Ser.	No Ser.	Low	0.13 (-0.26-0.51)	
	6	6	Energy Healing	232	232	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	0.21 (-0.20-0.61)	
	17	17	Herbal	1206	1078	Ser	Ser.	Ser.	No Ser.	Ser.	Low	0.47 (0.20-0.75)	
	14	14	Mind-Body Based	1072	546	V. Ser.	Ser.	Ser.	Ser.	Ser.	Very Low	0.29 (-0.01-0.59)	
Overall Response	**44**	**56**		**3033**	**2340**						**Low**	**RR**	**NNT**
	5	6	Body-Based	145	125	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	1.32 (0.89- 1.95	8 (3-23)
	7	7	Dietary Supplements	225	207	Ser.	No Ser.	No Ser.	No Ser.	No Ser.	Moderate	1.95 (1.02-3.73)	4 (2-189)
	3	4	Energy Healing	151	148	V. Ser.	No Ser.	No Ser.	Ser.	No Ser.	Low	1.32 (0.99- 1.76)	10 (4-303)
	20	20	Herbal	1506	1327	Ser.	No Ser.	No Ser.	No Ser.	Ser.	Moderate	1.57 (1.31-1.88)	5 (4-9)
	12	12	Mind-Body Based	1006	533	V. Ser.	No Ser.	No Ser.	No Ser.	Ser.	Low	1.67 (1.13-2.49)	5 (3-25)

Note: totals of articles and RCTs do not amount to the sum of the included studies as several articles include multiple RCTs from different CAM categories. Body-Based = relaxation, etc. Dietary Supplements = Aloe Vera, etc. Energy-Healing = acupuncture, etc. Herbal = Curcuma, Tong-Xie, etc. Mind-Body Based = Cognitive Behavioral Therapy, Hypnotherapy, etc. V. = Very, Ser. = Ser.

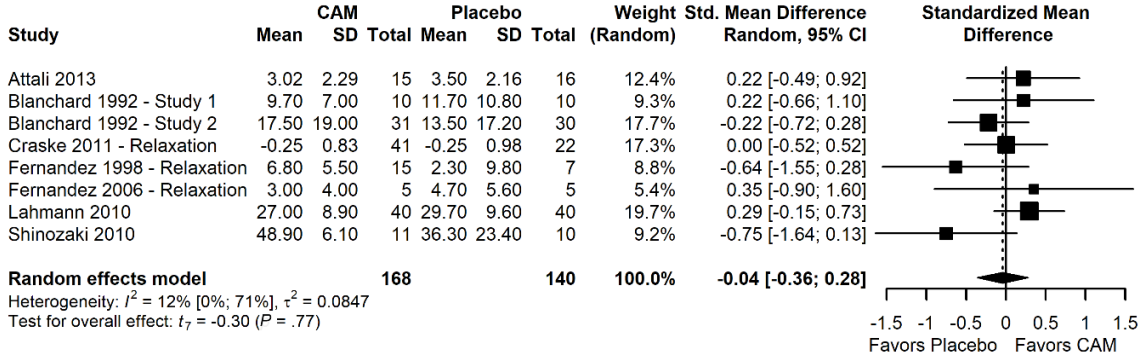

Study
CAM Mean SD Total
Placebo Mean SD Total
Weight (Random)
Std. Mean Difference Random, 95% CI
Standardized Mean Difference
Curcuma
Alt 2017 -113.00 64.90 43 -38.70 64.50 47 6.0% 1.15 [0.70; 1.59]
Brinkhaus 2005 0.55 10.54 48 -0.30 9.90 58 6.3% -0.08 [-0.47; 0.30]
Portincasa 2016 127.80 77.40 58 195.50 88.00 59 6.3% 0.82 [0.44; 1.19]
Random effects model 149 164 18.5% 0.62 [-0.95; 2.19]
Heterogeneity: I^2 = 89% [71%; 96%], τ^2 = 0.3446
Tong-Xie
Chen 2018 3.30 1.00 80 4.10 1.10 80 6.5% 0.76 [0.44; 1.08]
Fan 2017 3.54 1.46 348 4.21 1.54 348 7.1% 0.45 [0.30; 0.60]
Leung 2006 1.25 0.75 60 1.25 0.75 59 6.4% 0.00 [-0.36; 0.36]
Pan 2009 2.82 0.38 77 2.70 0.24 40 6.2% -0.35 [-0.74; 0.03]
Random effects model 565 527 26.2% 0.23 [-0.54; 0.99]
Heterogeneity: I^2 = 88% [70%; 95%], τ^2 = 0.2033
Other
Acosta 2016 13.95 3.94 20 16.12 3.25 20 5.1% 0.60 [-0.03; 1.23]
Bensoussan 1998 104.45 69.81 81 150.00 81.60 35 6.2% 0.62 [0.22; 1.02]
Kazemian 2017 29.25 14.53 20 51.59 13.92 22 4.8% 1.57 [0.88; 2.26]
Ko 2013 17.97 18.35 14 24.61 14.87 12 4.4% 0.39 [-0.38; 1.17]
Lee 2019 -2.71 2.34 19 -1.94 1.57 17 4.9% 0.38 [-0.28; 1.04]
Madisch 2005 29.13 20.92 154 45.20 22.60 52 6.5% 0.75 [0.43; 1.08]
Peckham 2014 -69.94 114.75 16 -13.57 78.77 60 5.4% 0.65 [0.08; 1.21]
Saito 2010 80.25 40.25 35 53.25 31.25 35 5.8% -0.75 [-1.23; -0.26]
Sallon 2002 1.40 0.58 34 1.80 1.04 27 5.6% 0.49 [-0.02; 1.00]
Tang 2018 113.62 62.49 99 166.35 71.33 107 6.7% 0.78 [0.50; 1.07]
Random effects model 492 387 55.4% 0.54 [0.14; 0.93]
Heterogeneity: I^2 = 77% [58%; 88%], τ^2 = 0.2431
Random effects model 1206 1078 100.0% 0.47 [0.20; 0.75]
Heterogeneity: I^2 = 82% [73%; 89%], τ^2 = 0.2460
Residual heterogeneity: I^2 = 83% [73%; 89%]
Test for overall effect: t_{16} = 3.61 (P = .002)
-2 -1 0 1 2
Favors Placebo Favors CAM


Study
CAM
Mean SD Total
Placebo
Mean SD Total
Weight (Random)
Std. Mean Difference
Random, 95% CI
Standardized Mean Difference
CBT
Blanchard 2007 4.20 1.50 60 4.00 1.90 22 7.6% -0.12 [-0.61; 0.37]
Craske 2011 - CBT -0.54 0.74 47 -0.25 0.98 22 7.4% 0.35 [-0.16; 0.86]
Drossman 2003 9.52 6.48 144 10.13 7.50 71 8.9% 0.09 [-0.20; 0.37]
Hunt 2009 35.00 12.00 28 52.00 14.00 26 6.9% 1.31 [0.72; 1.90]
Jang 2014 4.79 2.85 42 7.43 4.25 39 7.8% 0.73 [0.28; 1.19]
Lackner 2018 -74.11 16.90 291 -78.88 14.30 145 9.3% -0.30 [-0.50; -0.10]
Ljotsson 2010 1.40 1.50 42 2.40 1.60 43 7.9% 0.64 [0.21; 1.08]
Tkachuk 2003 1.07 0.86 14 1.08 0.91 14 5.9% 0.01 [-0.73; 0.75]
Random effects model 668 382 61.6% 0.31 [-0.12; 0.75]
Heterogeneity: I^2 = 85% [72%; 92%], τ^2 = 0.2189
Hypnotherapy
Filk 2019 254.51 92.14 288 269.40 83.40 54 8.8% 0.16 [-0.13; 0.45]
Lindfors 2012 - Study 1 11.80 4.60 45 13.20 3.30 45 8.1% 0.35 [-0.07; 0.77]
Simren 2004 35.40 3.90 14 33.50 2.60 14 5.8% -0.57 [-1.33; 0.18]
Random effects model 347 113 22.7% 0.07 [-0.99; 1.12]
Heterogeneity: I^2 = 52% [0%; 86%], τ^2 = 0.1323
Other
Fernandez 1998 - Behavior 3.10 5.80 16 2.30 9.80 7 5.0% -0.11 [-1.00; 0.78]
Fernandez 2006 - Behavior 6.20 6.10 5 17.60 9.00 5 2.9% 1.48 [0.08; 2.88]
Gaylord 2011 35.00 28.24 36 50.49 28.85 39 7.8% 0.54 [0.08; 1.00]
Random effects model 57 51 15.7% 0.48 [-1.05; 2.01]
Heterogeneity: I^2 = 35% [0%; 79%], τ^2 = 0.2540
Random effects model 1072 546 100.0% 0.29 [-0.01; 0.59]
Heterogeneity: I^2 = 78% [63%; 87%], τ^2 = 0.2208
Residual heterogeneity: I^2 = 79% [64%; 88%]
Test for overall effect: t_{13} = 2.06 (P = .06)
-2 -1 0 1 2
Favors Placebo
Favors CAM

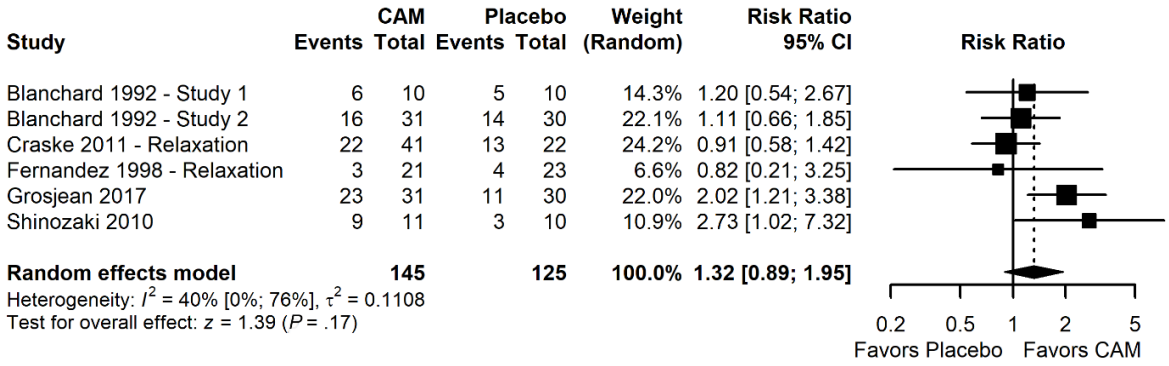

Study
CAM Events Total
Placebo Events Total
Weight (Random)
Risk Ratio 95% CI
Risk Ratio
Curcuma
Alt 2017 38 43 21 47 6.0% 1.98 [1.41; 2.77]
Brinkhaus 2005 26 52 30 67 5.6% 1.12 [0.76; 1.63]
Portincasa 2016 37 60 16 61 5.0% 2.35 [1.48; 3.75]
Random effects model 155 175 16.6% 1.72 [1.11; 2.65]
Heterogeneity: I^2 = 73% [8%; 92%], τ^2 = 0.1069
Tong-Xie
Chen 2018 46 80 30 80 5.9% 1.53 [1.09; 2.15]
Fan 2017 192 348 90 348 6.9% 2.13 [1.74; 2.61]
Leung 2006 19 60 20 59 4.7% 0.93 [0.56; 1.56]
Pan 2009 64 80 34 40 7.0% 0.94 [0.79; 1.12]
Wang 2006 25 30 12 30 5.0% 2.08 [1.31; 3.32]
Random effects model 598 557 29.5% 1.44 [1.01; 2.05]
Heterogeneity: I^2 = 91% [81%; 95%], τ^2 = 0.1340
Other
Bensoussan 1998 47 81 11 35 4.6% 1.85 [1.09; 3.12]
Bensoussan 2015 37 61 28 64 5.9% 1.39 [0.98; 1.95]
Ko 2013 8 14 4 12 2.6% 1.71 [0.68; 4.30]
Lee 2019 9 19 7 17 3.3% 1.15 [0.55; 2.41]
Madisch 2005 96 156 20 52 5.8% 1.60 [1.11; 2.31]
Merat 2010 14 45 6 45 2.8% 2.33 [0.98; 5.53]
Saito 2010 11 35 21 35 4.4% 0.52 [0.30; 0.92]
Sallon 2002 25 42 8 38 3.7% 2.83 [1.46; 5.49]
Su 2013 110 120 59 120 6.9% 1.86 [1.54; 2.25]
Tang 2018 59 109 38 107 6.2% 1.52 [1.12; 2.07]
Vejdani 2006 8 14 4 18 2.4% 2.57 [0.97; 6.82]
Yadav 1989 37 57 17 52 5.2% 1.99 [1.29; 3.07]
Random effects model 753 595 53.8% 1.61 [1.25; 2.07]
Heterogeneity: I^2 = 56% [15%; 77%], τ^2 = 0.1249
Random effects model 1506 1327 100.0% 1.57 [1.31; 1.88]
Heterogeneity: I^2 = 77% [64%; 85%], τ^2 = 0.1143
Residual heterogeneity: I^2 = 77% [65%; 86%]
Test for overall effect: z = 4.88 (P < .001)
0.2
0.5
1
2
5
Favors Placebo
Favors CAM


Identification
Screening
Eligibility
Included
Records identified through database searching after duplicates removed (n = 2276)
Records screened (n = 2276)
Records excluded (n = 1912)
Full-text articles assessed for eligibility (n = 220)
Full-text articles excluded (n = 154)
•31 excluded due to no extractable data
•63 excluded due to no placebo
•3 excluded due to lack of randomization
•3 excluded that were not IBS
•9 excluded that were cross-over studies without usable data
•1 excluded due to not being long enough in duration
•15 excluded as a duplicate data set
•28 excluded that were not available in English
Studies included in meta-analysis (n = 66)*
Body-based (n = 8)
Dietary supplements (n = 15)
Energy-healing (n = 7)
Herbal (n = 23)
Mind-body based (n = 16)
*3 studies include trials of multiple complementary alternative medicine therapies

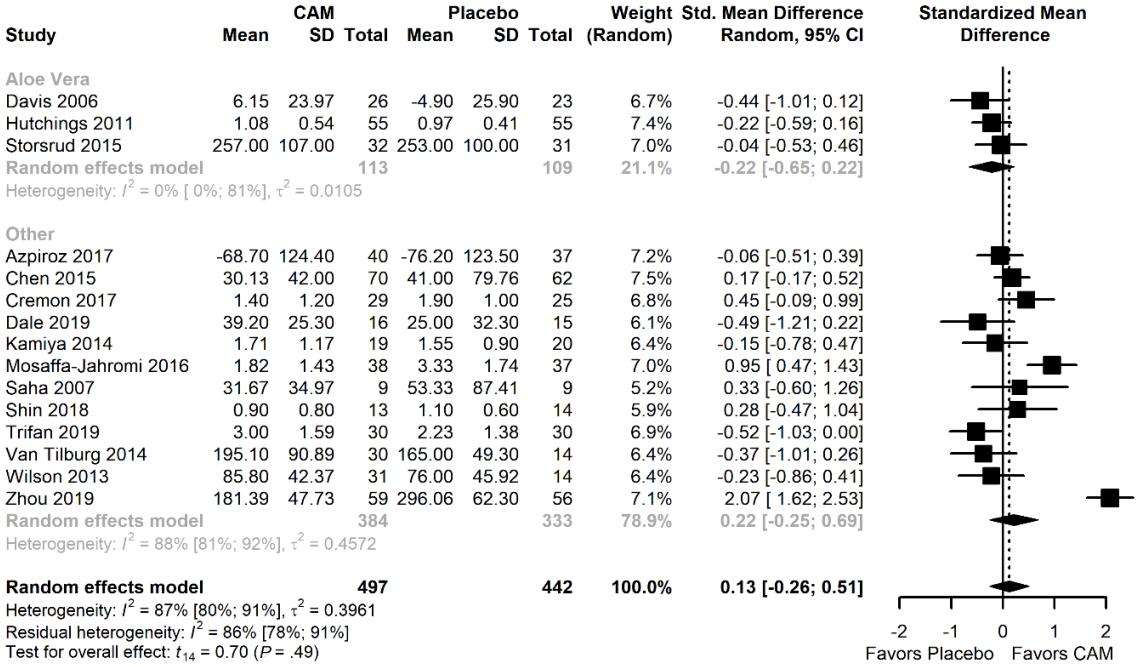
Supplementary Figure 1: Forest plot of studies of body-based therapy vs placebo or sham with effect on abdominal pain



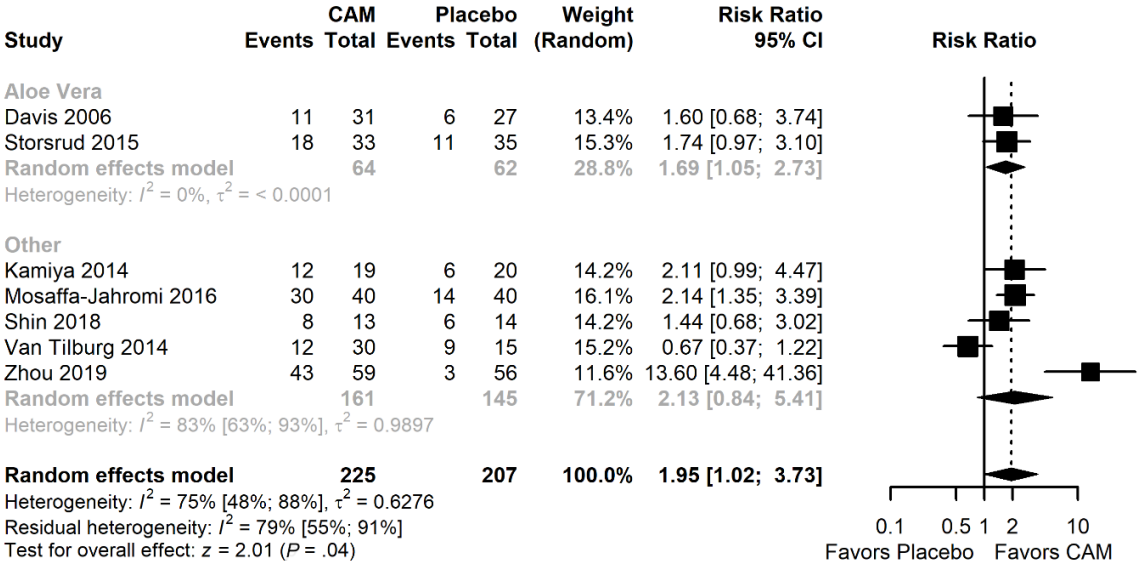
Supplementary Figure 2: Forest plot of studies of body-based therapy vs. placebo or sham with effect on overall response



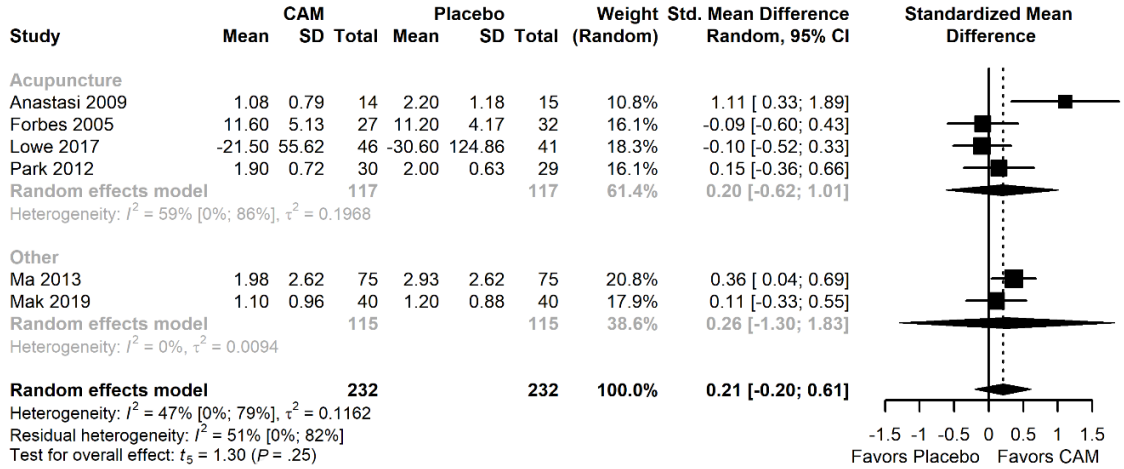
Supplementary Figure 3: Forest plot of studies of dietary supplement vs placebo or sham with effect on abdominal pain by type of intervention (between group p-value = 0.068)



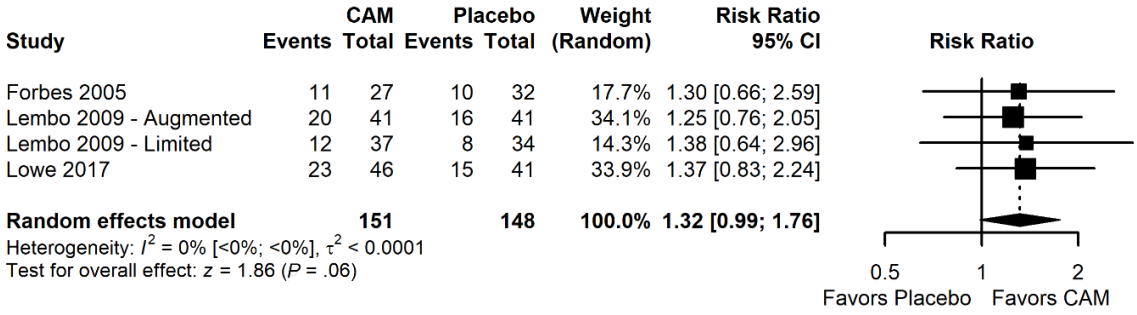
Supplementary Figure 4: Forest plot of studies of dietary supplement vs placebo or sham with effect on overall response by type of intervention (between group p-value = 0.67):



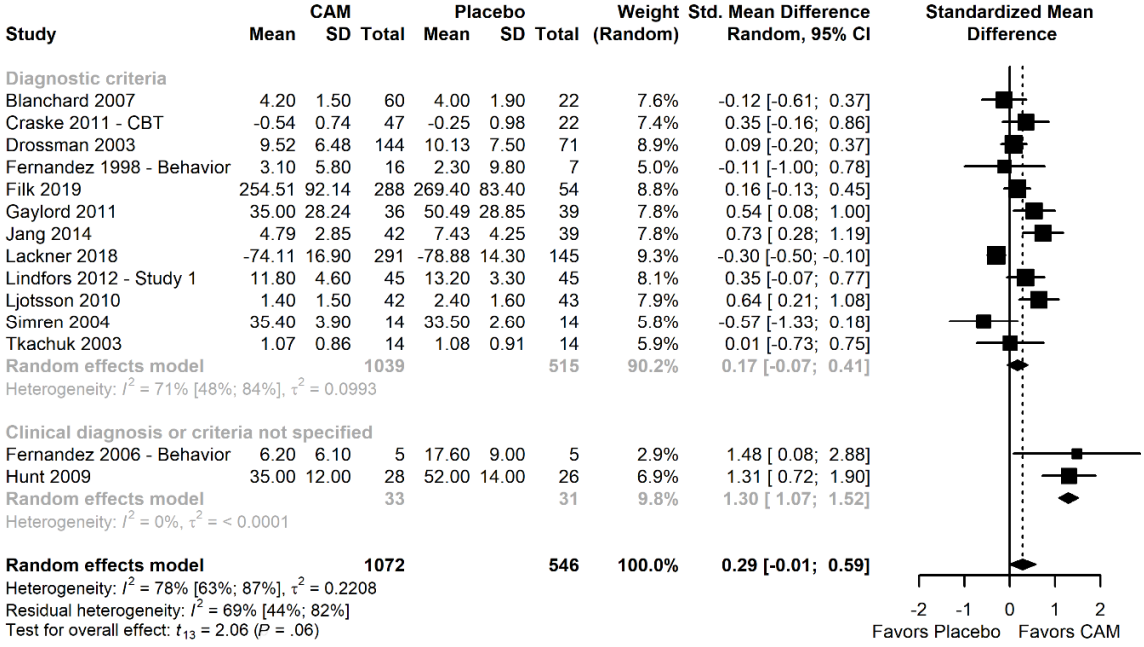
Supplementary Figure 5: Forest plot of studies of energy-healing vs placebo or sham with effect on abdominal pain by type of intervention (between-group p-value = 0.81)



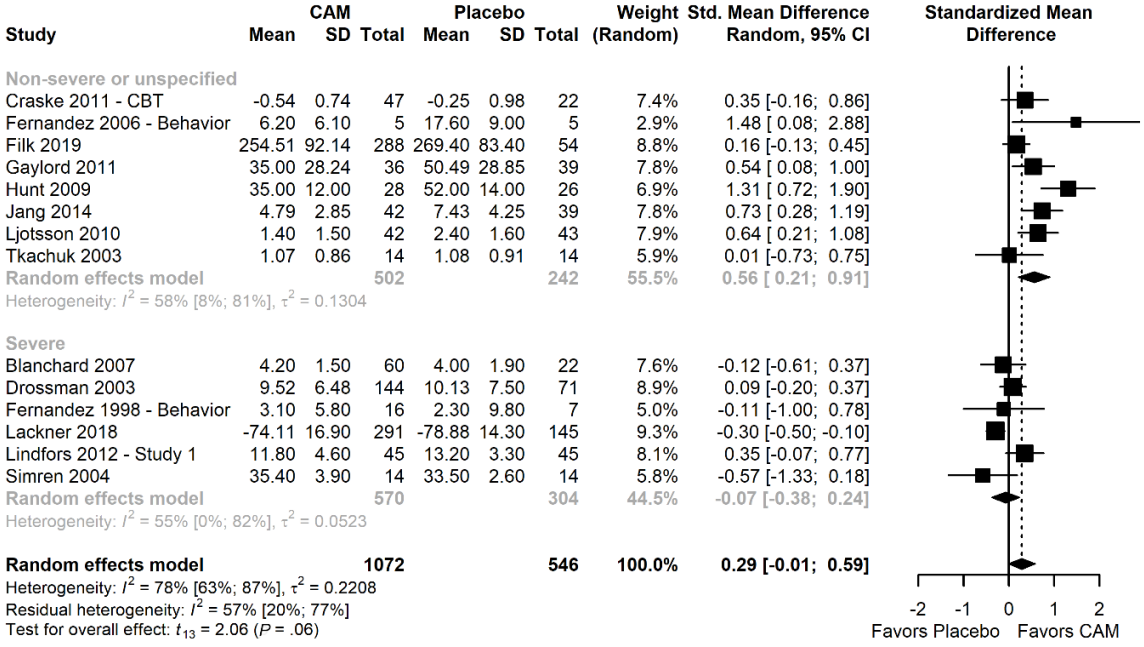
Supplementary Figure 6: Forest plot of studies of energy-healing vs. placebo or sham with effect on overall response



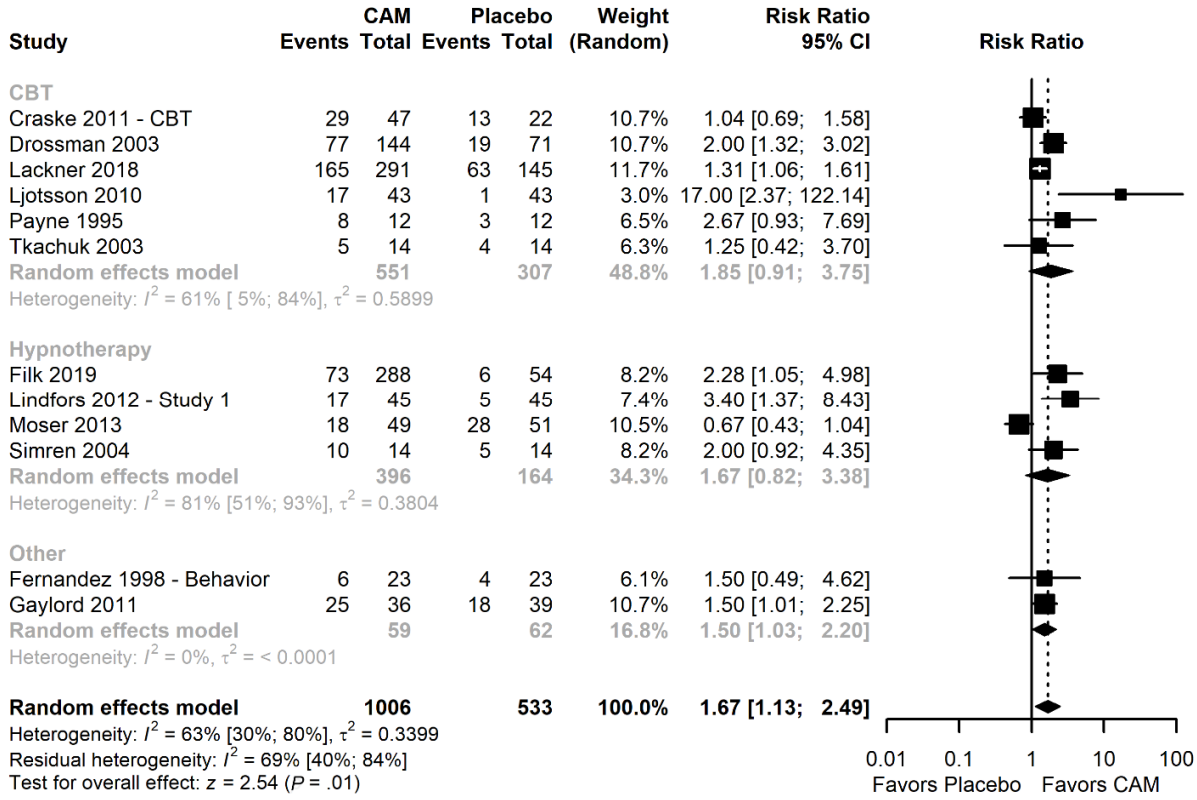
Supplementary Figure 7: Forest plot of studies of mind-body based therapy vs placebo or sham with effect on abdominal pain by IBS definition (between-group p-value < 0.001)



Supplementary Figure 8: Forest plot of studies of mind-body based therapy vs placebo or sham with effect on abdominal pain by IBS severity (between-group p-value < 0.001)



Supplementary Figure 9: Forest plot of studies of mind-body based therapy vs placebo or sham with effect on overall response by intervention (between group p-value = 0.87)



Study Eligibility: The review was limited to trials with a minimum duration of two weeks of therapy. First-period data from cross-over trials were also eligible. Studies investigating other organic gastrointestinal conditions such as inflammatory bowel disease, microscopic colitis, and celiac disease and trials without an appropriate placebo or sham control group were excluded. The diagnosis of IBS was determined using any definition provided by the study including symptom-based diagnostic criteria.

Supplementary Table 1: Risk of bias assessment

Study ID	Randomization (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Outcome Assessment Blinding (Detection Bias)	Loss to follow-up (Selection Bias)	Intention-to-treat Analysis (Attrition Bias)	Missing Data (Attrition Bias)	Selective Reporting Bias	Overall RISK
Body-Based									
Attali 2013	L	U	H	L	L	L	L	L	M
Blanchard 1992 - Study 1	U	U	U	U	L	L	L	L	H
Blanchard 1992 - Study 2	U	U	U	U	H	L	L	L	H
Craske 2011 - Relaxation	L	L	H	L	H	L	L	L	M
Fernandez 1998 - Relaxation	U	U	U	U	H	H	H	L	H
Fernandez 2006 - Relaxation	U	U	U	U	L	L	L	H	H
Grosjean 2017	L	U	H	L	L	M	M	L	M
Lahmann 2010	L	L	U	U	L	L	L	L	H
Shinozaki 2010	U	U	H	L	L	L	L	L	M
Dietary Supplement									
Azpiroz 2017	L	U	L	L	L	M	M	L	L
Chen 2015	U	U	L	L	M	H	H	L	H
Cremon 2017	L	L	L	L	L	L	L	L	L
Dale 2019	U	U	L	L	M	H	H	L	H
Davis 2006	L	U	L	L	M	L	L	L	L
Hutchings 2011	U	U	L	L	H	L	L	H	H
Kamiya 2014	L	U	L	L	L	M	M	L	L
Mosaffa-Jahromi 2016	L	U	L	L	L	L	L	L	L
Saha 2007	U	U	L	L	L	L	L	L	M
Shin 2018	L	L	L	L	L	L	L	L	L
Storsrud 2015	L	L	L	L	M	L	L	L	L
Trifan 2019	L	U	L	L	L	L	L	L	L
Van Tilburg 2014	U	U	L	L	L	M	M	L	H
Wilson 2013	U	U	L	L	H	H	M	L	H
Zhou 2019	L	L	L	L	M	H	H	L	H
Energy-healing									
Anastasi 2009	U	U	M	L	H	H	H	L	H
Forbes 2005	L	L	M	L	M	L	L	L	M
Lembo 2009 - Augmented	L	U	M	L	L	L	L	L	M
Lembo 2009 - Limited	L	U	M	L	M	L	L	L	M
Lowe 2017	L	U	M	L	M	H	H	L	H
Ma 2013	L	U	M	L	L	L	L	L	M
Mak 2019	L	L	M	L	L	L	L	L	M

Park 2012	L	U	M	L	H	H	H	L	H
Herbal									
Acosta 2016	U	U	L	M	L	L	L	L	M
Alt 2017	L	U	L	L	L	L	L	L	L
Bensoussan 1998	L	L	L	L	M	L	L	L	L
Bensoussan 2015	L	L	L	L	M	L	L	L	L
Brinkhaus 2005	L	L	L	L	L	L	L	L	L
Chen 2018	L	L	L	L	L	L	L	L	L
Fan 2017	L	H	H	L	H	L	L	L	H
Kazemian 2017	L	U	H	H	H	H	H	L	H
Ko 2013	L	L	L	L	L	L	L	L	L
Lee 2019	L	L	L	L	H	L	L	L	L
Leung 2006	L	L	L	M	H	L	L	H	H
Madisch 2005	L	L	L	L	L	L	L	L	L
Merat 2010	L	U	L	L	H	H	H	L	H
Pan 2009	L	U	L	L	L	M	M	L	M
Peckham 2014	L	L	H	H	M	H	H	L	H
Portincasa 2016	L	U	L	L	L	M	M	L	H
Saito 2010	L	L	L	L	M	L	L	L	L
Sallon 2002	L	U	L	M	H	L	L	L	H
Su 2013	U	U	L	L	L	M	M	H	H
Tang 2018	L	U	L	L	L	M	M	L	H
Vejdani 2006	L	H	L	L	M	L	L	H	H
Wang 2006	L	L	L	L	M	L	L	H	H
Yadav 1989	L	U	L	L	H	H	H	L	H
Mind-Body Based									
Blanchard 2007	U	U	U	U	M	L	L	L	H
Craske 2011 - CBT	L	L	H	L	H	L	L	L	M
Drossman 2003	L	L	H	U	H	L	L	L	H
Fernandez 1998 - Behavior	U	U	U	U	H	H	H	L	H
Fernandez 2006 - Behavior	U	U	U	U	L	L	L	H	H
Filk 2019	L	U	H	L	H	L	L	L	H
Gaylord 2011	L	U	U	L	M	L	L	L	H
Hunt 2009	L	U	U	U	H	L	L	L	H
Jang 2014	L	L	H	H	M	H	H	L	H
Lackner 2018	L	L	H	L	M	L	L	L	M
Lindfors 2012 - Study 1	L	L	H	U	L	L	L	L	H
Ljotsson 2010	L	L	H	U	M	L	L	L	H
Moser 2013	L	M	H	H	M	H	H	L	H
Payne 1995	U	U	H	U	L	L	L	L	H
Simren 2004	L	L	H	H	M	H	H	L	H
Tkachuk 2003	L	U	H	U	H	H	H	L	H

Note: L=low risk of bias, M=moderate risk of bias, H=high risk of bias, U=unclear risk of bias

Supplementary Table 2: Subgroup Analyses

Outcome	Intervention	Subgroups		No. of Studies	No. of Patients	RR (95% CI)	p
Overall Response	Body-Based	Risk of Bias	Moderate	3	145	1.57 (0.83; 2.98)	0.36
			High	3	125	1.10 (0.72; 1.67)	
	Dietary Supplement	Intervention	Aloe Vera	2	126	1.69 (1.05; 2.73)	0.67
			Other	5	306	2.13 (0.84; 5.41)	
		Risk of Bias	Low	5	272	1.86 (1.39; 2.48)	0.76
			High	2	160	2.90 (0.16; 52.51)	
	Herbal Therapy	Intervention	Curcuma	3	330	1.72 (1.11; 2.65)	0.8
			Tong-Xie	5	1155	1.44 (1.01; 2.05)	
			Other	12	1348	1.61 (1.25; 2.07)	
		Risk of Bias	Low	9	950	1.37 (1.04; 1.79)	0.051
			High	10	1363	1.91 (1.56; 2.33)	
		Location	Europe	4	567	1.41 (0.95; 2.10)	0.6
			Asia	13	1955	1.73 (1.44; 2.06)	
			Australia	2	241	1.53 (1.10; 2.12)	
		IBS Definition	Diagnostic Criteria	17	2397	1.58 (1.29; 1.95)	0.81
			Not Specified	3	436	1.51 (1.08; 2.11)	
		IBS Type	C	2	105	1.86 (0.96; 3.59)	0.8
			D/M	9	1673	1.50 (1.20; 1.87)	
			Unspecified	9	955	1.62 (1.16; 2.24)	
		Study Duration	<8 weeks	8	1714	1.70 (1.37; 2.11)	0.37
			8+ weeks	12	1119	1.45 (1.10; 1.92)	
	Mind-Body Based	Intervention	CBT	6	858	1.85 (0.91; 3.75)	0.87
			Hypnotherapy	4	560	1.67 (0.82; 3.38)	
			Other	2	131	1.50 (1.03; 2.20)	
		Risk of Bias	Moderate	2	505	1.23 (0.97; 1.55)	0.12
			High	10	1034	1.87 (1.17; 2.99)	
		Location	North America	6	847	1.45 (1.11; 1.90)	0.39
			Europe	6	692	2.09 (0.94; 4.62)	
		IBS Severity	Unspecified	6	624	1.95 (0.96; 3.96)	0.55
			Severe	6	915	1.51 (0.97; 2.35)	
Abdominal Pain	Body-Based	Risk of Bias	Moderate	3	115	-0.11 (-1.21; 0.99)	0.7
			High	5	193	0.01 (-0.45; 0.46)	
	Dietary Supplements	Intervention	Aloe Vera	3	222	-0.22 (-0.65; 0.22)	0.68
			Other	12	717	0.22 (-0.25; 0.69)	
		Risk of Bias	Low	8	444	0.06 (-0.35; 0.47)	0.79
			High	6	477	0.17 (-0.84; 1.18)	
		Location	North America	3	204	0.50 (-2.89; 3.90)	0.068
			Europe	7	444	-0.17 (-0.47; -0.13)	
			Asia	5	291	0.33 (-0.19; 0.85)	
		IBS Type	D/M	7	449	0.18 (-0.65; 1.01)	0.77
			Unspecified	8	490	0.07 (-0.33; 0.46)	
		IBS Severity	Unspecified	12	762	0.19 (-0.28; 0.66)	0.15

			Severe	3	177	-0.20 (-0.96; 0.55)	
		Study Duration	<8 weeks	9	483	-0.12 (-0.48; 0.23)	0.082
			8+ weeks	6	456	0.51 (-0.34; 1.37)	
	Energy Healing	Intervention	Acupuncture	4	234	0.20 (-0.62; 1.01)	0.81
			Other	2	230	0.26 (-1.30; 1.83)	
		Risk of Bias	Moderate	3	289	0.17 (-0.38; 0.73)	0.71
			High	3	175	0.31 (-1.16; 1.77)	
	Herbal	Intervention	Curcuma	3	313	0.62 (-0.95; 2.19)	0.52
			Tong-Xie	4	1092	0.23 (-0.54; 0.99)	
			Other	10	879	0.54 (0.14; 0.93)	
		Risk of Bias	Low	8	810	0.41 (-0.08; 0.90)	0.45
			Moderate	2	157	0.08 (-5.88; 6.04)	
			High	7	1317	0.63 (0.22; 1.03)	
		Study Location	North America	2	110	-0.09 (-8.54; 8.35)	0.67
			Europe	5	624	0.42 (-0.12; 0.96)	
			Asia	9	1434	0.60 (0.20; 1.00)	
		IBS Definition	Diagnostic Criteria	15	1972	0.49 (0.18; 0.79)	0.74
			Not Specified	2	312	0.34 (-4.95; 5.63)	
		IBS Type	D/M	7	1360	0.35 (-0.04; 0.74)	0.71
			Unspecified	9	863	0.57 (0.07; 1.07)	
		Study Duration	<8 weeks	6	1336	0.50 (0.04; 0.96)	0.85
			8+ weeks	11	948	0.45 (0.04; 0.86)	
	Mind-Body Based	Intervention	CBT	8	1050	0.31 (-0.12; 0.75)	0.58
			Hypnotherapy	3	460	0.07 (-0.99; 1.12)	
			Other	3	108	0.48 (-1.05; 2.01)	
		Risk of Bias	Moderate	2	505	-0.02 (-4.07; 4.03)	0.31
			High	12	1113	0.34 (0.01; 0.66)	
		Location	North America	7	959	0.24 (-0.24; 0.72)	0.99
			Europe	6	578	0.24 (-0.32; 0.80)	
		IBS Definition	Diagnostic Criteria	12	1554	0.17 (-0.07; 0.41)	<0.001
			Not Specified	2	64	1.30 (1.07; 1.52)	
		IBS Severity	Unspecified	8	744	0.56 (0.21; 0.91)	<0.001
			Severe	6	874	-0.07 (-0.38; 0.24)	
		Study Duration	<8 weeks	3	146	0.74 (-1.39; 2.87)	0.29
			8+ weeks	11	1472	0.20 (-0.06; 0.46)	